IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
Civil No. 2:16-cv-01118-CCC-JBC

IMMUNEX CORPORATION; AMGEN MANUFACTURING, LIMITED; and HOFFMAN-LaROCHE INC., Plaintiffs, v. SANDOZ INC.; SANDOZ INTERNATIONAL GMBH; SANDOZ GMBH, Defendants.	TRANSCRIPT OF PROCEEDINGS - TRIAL - AM SESSION

Newark, New Jersey
September 24, 2018

B E F O R E:

THE HONORABLE CLAIRE C. CECCHI,
UNITED STATES DISTRICT JUDGE

Pursuant to Section 753 Title 28 United States Code, the following transcript is certified to be an accurate record as taken stenographically in the above entitled proceedings.

S/WALTER J. PERELLI

WALTER J. PERELLI, CCR, CRR
Official Court Reporter

A P P E A R A N C E S:

WALSH PIZZI O'REILLY FALANGA LLP
BY: LIZA M. WALSH, ESQ.
MARC D. HAEFNER, ESQ.
COLLEEN M. MAKER, ESQ.
- and -
SIDLEY AUSTIN LLP
BY: VERNON M. WINTERS, ESQ.
DAVID T. PRITIKIN, ESQ.
STEVEN J. HOROWITZ, ESQ.
SUE WANG, ESQ.
JEFFREY P. KUSHAN, E SQ.
Attorneys for Plaintiffs Immunex Corporation and Amgen Manufacturing Limited

J. DREW DIAMOND, ESQ.
Amgen Corporate Counsel

GIBBONS P.C.
BY: CHARLES H. CHEVALIER, ESQ.
- and -
WILLIAMS & CONNOLLY LLP
BY: AARON MAURER, ESQ.
Attorneys for Plaintiffs Hoffman-LaRoche, Inc.

A P P E A R A N C E S (cont'd):

HILL WALLACK LLP
BY: CHRISTY L. SAVERIANO, ESQ.
- and -
WINSTON & STRAWN LLP
BY: MAUREEN L. RURKA, ESQ.
GEORGE C. LOMBARDI, ESQ.
JULIA MANO JOHNSON, ESQ.
DAN H. HOANG, ESQ.
LOREN G. RENE, ESQ.
KARALENA M. GUERRIERI, ESQ.
Attorneys for Defendant Sandoz

ALSO IN ATTENDANCE:
Mr. Steart Watt, Plaintiffs' Representative

I N D E X

WITNESS	DIRECT	CROSS
ARNE SKERRA		
By Ms. Rurka	28	
By Mr. Winters		68

E X H I B I T S

EXHIBIT	IN EVIDENCE
PTX-165; PTX-181; PTX-182; PTX-313; PTX-315; PTX-317; PTX-320; PTX-383; PTX-390; PTX-6.14; PTX-6.280; PTX-6.332; PTX-6.456; PTX-7351; PTX-7.416; DTX-460; PTX-748, PTX-1407	5

9:13A

THE DEPUTY CLERK: All rise.

THE COURT: Good morning, everyone. Have a seat. Please good morning. How are you?

MR. RURKA: Good morning.

MR. WINTERS: Good morning, your Honor.

THE COURT: We're on Immunex Corporation, et al versus Sandoz Inc, et al, it's Civil Action 16-1118.

Let's have appearances, please.

(Appearances are placed on the record by Counsel.)

THE COURT: Good morning. Thank you all.

Should we start with exhibits today?

MR. HAEFNER: Before we even get to the exhibits, your Honor, I do have a little bit of housekeeping --

THE COURT: Yes, go ahead.

MR. HAEFNER: -- from Friday. I do have for your Honor for the Lesslauer Volume 2 deposition, a copy of the designation time report that we had been providing.

9:15A THE COURT: Good. You can hand that up.

MR. HAEFNER: So I will bring a copy up, if that's all right.

THE COURT: Thank you, yes.

MR. HAEFNER: And then we do have an exhibit list, your Honor.

THE COURT: Great.

MR. HAEFNER: Now, one of the exhibits that was going

to be on this list is a subject of continuing dispute.

THE COURT: Which one?

MR. HAEFNER: Or perhaps not.

THE COURT: Or perhaps not? Okay. We can start the day that way.

(Laughter.)

MR. HAEFNER: So it is PTX-622, your Honor.

THE COURT: What is 622?

MR. HAEFNER: This is an answer to an interrogatory.

THE COURT: Okay.

MR. HAEFNER: And there was some confusion last night at the meet/confer, it was late at night, your Honor, about who was going to get back to whom about it. So Ms. Johnson has not had an opportunity --

9:17A THE COURT: Do you want to just take a moment to look at it together and you can tell me what's going on?

MS. RENE: Yes. Good morning, your Honor. We had discussed it --

THE COURT: Good morning.

MS. RENE: -- this morning. For the first time Plaintiffs indicated a potential basis for including it, and we haven't had an opportunity to look at that. So I think what we discussed was that we mutually agreed to take a look at that day and revisit it later today.

THE COURT: Do you want to hold onto that and we can

talk about it later?

MS. RENE: Yes.

MR. HAEFNER: And if we have to close the case, your Honor, and Sandoz does, in fact, rest today, we will revisit it at the end of the day necessarily. But --

THE COURT: That's fine. You can look at it today and I'm sure you'll be able to come to some sort of conclusion on it.

MS. RENE: All right.

MR. HAEFNER: But I'm going to cross it off for now, your Honor, and pass you the remainder of the list.

THE COURT: That's fine.

Is there any objection to the remainder of the list?

MS. RENE: No.

THE COURT: Have you gone through it?

MS. RENE: We've gone through it and we have no objection to the remainder, your Honor.

THE COURT: Let's hear the list.

MR. HAEFNER: So the its list, your Honor, from Plaintiffs is PTX-165; PTX-181; PTX-182; PTX-313; PTX-315; PTX-317; PTX-320; PTX-383; PTX-390; PTX-6.14; PTX-6.280; PTX-6.332; PTX-6.456; PTX-7351; PTX-7.416; and from Defendants: DTX-460; PTX-748, and PTX-1407.

9:18A THE COURT: Okay. Any objection to the list?

MS. RENE: No objection, your Honor.

THE COURT: Okay.

(Above recited exhibits are received in evidence.)

THE COURT: If you just want to give me a little preview on 622. I know you're still thinking about it, but what is the potential issue there?

MS. RENE: Yes, your Honor. So 622 is a response, an interrogatory response, it hasn't hasn't been used yet with any witnesses and, so we still have to take a look at that to see if there's a valid basis for its admission.

9:19A THE COURT: Mr. Haefner, with respect to that, counsel has indicated she's going to take a look at it but it hasn't been used yet. Is that really the assertion, is that the assertion?

MS. RENE: Yes, your Honor.

THE COURT: Okay.

MR. HAEFNER: And the argument in response, your Honor, is that the answer to interrogatories is a judicial admission, and under Rule 33 the answer to interrogatory rule, it's admissible on its face with or without a sponsoring witness.

THE COURT: I'm sorry, I missed the end of what you just said.

MR. HAEFNER: It's admissible on its face under Rule 33 as an admission without a sponsoring witness.

THE COURT: Without a sponsoring witness.

Counsel, they're certified, are they not?

MS. RENE: That's right. So we haven't had -- counsel just raised that as a basis for admission this morning. We haven't had a chance to look at that.

THE COURT: Take a look at it.

MS. RENE: Yes.

THE COURT: Okay. Thank you. Anything else?

MR. HAEFNER: Again, just for housekeeping, your Honor, we do have, after we play Dr. Alliger later today as a deposition, we do have the clip reports, JTX-81, 82, and 83 to move into evidence, and I'm just mentioning it now as a reminder to all of to us actually do that before the close of the case today.

9:21A THE COURT: Okay.

MR. HAEFNER: If it closes today.

THE COURT: Let's talk about the schedule. Do we think it will be closing today?

MR. RURKA: Your Honor, we have a witness that we're taking out of order from our rebuttal reply case, Dr. Skerra, that will be going first thing this morning.

THE COURT: And if I remember, it was about an hour and a half.

MR. RURKA: At the most. I think it's probably about an hour, maybe a little bit more but not much more so. I'm not sure how long the cross is.

THE COURT: That's fine.

MR. RURKA: But after that I believe that they have that to finish up their case.

THE COURT: What do we expect after that witness?

MS. WALSH: Our goal and certainly our hope was to finish today after Dr. Skerra we have Stu Watt, which we believe is going to be probably about half an hour, 35 minutes on direct.

THE COURT: Then it looks like we have a clip after that?

MS. WALSH: That's correct, which is 33 minutes.

THE COURT: Okay. Anything else or is that really it?

MS. WALSH: Then we will be resting at this portion of it, we may have rebuttal tomorrow. But we'll see how the day goes.

9:22A THE COURT: Yes. And in terms of tomorrow, I spoke with Jacquie, I believe one witness needs a remote video clip or an examination through a video. Correct?

MS. WALSH: That's correct.

THE COURT: And our.

MS. RURKA: The folks are working on that right now. So we'll keep you posted. It should be fine.

MS. WALSH: We appreciate it.

MR. RURKA: We will have one more witness after Dr. Skerra, that would be Dr. DeForest McDuff, and that should be a

very short, maybe 20 minutes to a half hour.

THE COURT: That sounds fine. Excellent. Thanks so much.

Is there anything else in terms of housekeeping or should we start the day?

MR. HAEFNER: In anticipation of Mr. Watt's testimony, we do have a dispute about that, about an exhibit that we hope to do now, and there's also a dispute about a document to be introduced through the deposition testimony of Dr. Arora in Sandoz's case that we were intending to do now, your Honor, because it would affect which clips get played.

9:23A THE COURT: All right. Go ahead.

MR. HAEFNER: Its up -- you know.

THE COURT: Go ahead.

MR. HAEFNER: Okay. So as to Mr. Watt, your Honor, there's a European patent. The majority of it is in German, but portions of it are in English, and then, of course, there are numbers on it that indicate various things; dates, other patents. Those are in numbers, not to be flip. But I mean, they're self-evident on their case what they are. We do not have a certified translation of it. It's not our intention to discuss any portion of it that is that in German. You know, Mr. Watt is not fluent in German.

THE COURT: How are you using it?

MR. HAEFNER: My understand, your Honor, is it's just

to show that it is, in fact, the thing it purports to be, in English. It's a European Patent Office patent and, you know, the desire is to use it in the course of the evidence simply for it being this thing.

9:24A THE COURT: Okay. But in terms of any specific examination of the contents therein, are you doing that?

MR. HAEFNER: Not of that German portions, your Honor. Yes, the claim at issue is in English, your Honor, I'm reminded, as are the various references.

THE COURT: Okay.

MR. HAEFNER: So, yes, just to repeat, there's no questioning on the areas that are in German.

THE COURT: What was that? There's no question that?

MR. HAEFNER: No questioning will be held on the areas that are in German.

THE COURT: Okay. Counsel.

MS. RENE: Your Honor, to provide some context for this dispute, we were first apprised of their intent to rely on this exhibit last Wednesday, and we objected on Thursday and requested that they provide us with a certified English translation for the Court's reference. The document that they are discussing is a European patent application. The entirety of the application is in German with the exception with one portion of the claims which appear to have an English translation related to it. It's not a certified copy itself,

and the entirety of the patent is in German.

9:25A So we raised this on Thursday during the meet-and-confer and requested a certified English translation of it so we can actually know what the patent is all about and what's disclosed in the specification. And the response to that was that they were only discussing the claims, which I think is what Mr. Haefner said this morning.

Our position is that it's unduly prejudicial. Well, it's not admissible under Rule 403 or 401 primarily because it's unduly prejudicial. If they're going to be talking about the claims, we have no idea what is in the specification. It's very difficult for us to -- it's actually impossible for us to prepare for cross-examination about what is potentially in these claims without having any sort of point of reference. And again, we did request the certified translation. They refused to give it to us. We requested it again last night, and again they refused to give it to us. We also believe it's a waste of the Court's time and resources. Again, the vast majority of this patent is in German.

And as Mr. Haefner --

9:26A THE COURT: Why is the patent half in German and half in English?

MS. RENE: It's a European patent so it's not actually half in German and half in English, the entirety is in German.

THE COURT: What portion of it is in English though?

MS. RENE: The claims.

THE COURT: Why are the claims in English?

MS. RENE: It's a European patent application, and at the end of the European Patent Applications the claims are actually in German and then the claims are in English and then the claims are in French. I believe that that's just the way that they are issues in Europe. But again, the vast majority of it is in German so we really don't know what the specification says. To to the extent that the witness is going to be testifying about what those claims mean or anything about what the patent means, we don't have the proper context for that. We also don't have a file history for this. It was never -- I don't believe that it was ever produced, certainly it wasn't on the exhibit list. So it's really impossible for us to sort of determine what these things mean.

THE COURT: Okay. Yes.

MR. PRITIKIN: Your Honor, I can clear up some of the mystery here.

9:27A THE COURT: Yes.

MR. PRITIKIN: So this is a patent that issued off the same application that led to the patents-in-suit. It's in the same family. It's part -- there was the original Roche filing, the Court will recall, back in 1990, and the original filing was in German, the specification.

Sandoz provided on the exhibit list a certified

translation of that. So the claim that they don't know what the German application says probably isn't quite right because they've translated it themselves and they put it in the record of the case, a certified translation of the specification, the same specification. And it's the application --

THE COURT: Did they provide a certified copy of the translation of exactly the same thing that you're offering now?

MR. PRITIKIN: The specification -- they issued off the same specification.

THE COURT: What about beyond the specification?

MR. PRITIKIN: I don't know there are differences in the specification between the two. So the patent issued, the claims are in English, and they know what's in the specification. We have -- it's in the '182 and the '522.

9:28A The questions that are going to be asked of Mr. Watt are limited to --

THE COURT: Let me get to that.

Was the patent in the same family translated already and is that a basis for us to move upon at this point?

MS. RENE: So, a patent in the same family was translated. It's the original patent, the original priority patent. However, we don't know that it has the same specification as the current patent that they're trying to admit.

If your Honor remembers, the patents-in-suit, they did

amend those specifications, both the '182 and the '522 were amended. We have no idea because we don't speak German, so we really don't know what's in the specification.

We cannot independently confirm that the specification of the patent that they're trying to use that's primarily in German is the same as the priority specification without a certified translation.

THE COURT: Well, let me ask Plaintiffs this: Isn't it very -- I mean shouldn't it be pretty straightforward to get a German translation of this?

9:29A MR. PRITIKIN: We already have it, your Honor, they provided it.

THE COURT: You're saying that's actually a different patent in the same family though. Correct?

MR. PRITIKIN: But there's no indication that it was ever amended. We have the whole file --

THE COURT: There's no indication it was ever?

MR. PRITIKIN: Amended in German. This all issued in the European Patent Office. We have the entire 121 file history. It was produced, this comes out of it. It's already in evidence.

THE COURT: You're saying it's exactly the same?

MR. PRITIKIN: As far as we know it's the same. I mean, if there was a change made you could tell from looking at the file history.

THE COURT: Is there any indication that there's any change from what's already been translated? Because that's really the issue.

MS. RENE: Right. So my understanding is the file history, that was produced and my understanding is that's in German as well. You know, so no one from -- I mean, unless it's a German speaker, I can't say for sure whether or not the specification was amended or not.

THE COURT: Is there anyone here that speaks German that could take a look at it real quick for us?

9:30A MR. PRITIKIN: Dr. Skerra.

THE COURT: That's the issue. We want to make sure that what needs to be translated was translated. But if it's already been done, then we can move on to something else. But if there's something in there that you believe has not been translated that's distinct, I'd like to know what it is and then we can address it.

MS. RENE: Sure. You know, it's the simple fact that we can't independently confirm without a certified translation. And again this goes back to Wednesday. They knew since last week that they were going to be using this and they had ample opportunity to provide with us a certified translation.

THE COURT: Let's get back to this though. The claims themselves, it sounds like they're in different languages, they're repeated. To the extent we're looking at, and sort of

keeping our thrust to those particular claims, do we need anything beyond that if it appears that the thing has already been translated previously?

MS. RENE: I mean, the claims mean what they mean, but to the extent the witness is going to be interpreting those and say that they cover certain things, we believe that's improper without a certified --

9:32A THE COURT: But those claims are in English, are they not?

MS. RENE: That's right, the claims do appear in English although the translation is a little -- to use a legal term, "wonky."

So it's a little bit difficult to read. But again, to the extent that the witness is going to be testifying as to claims covering certain things, you know, without the proper context it's -- we believe it's unduly prejudicial and it's also not particularly useful for the Court.

THE COURT: Tell me again how you're going to be using this.

MR. PRITIKIN: So the patent -- could I have just a second, your Honor?

9:33A THE COURT: Yes.

MR. PRITIKIN: Your Honor, this is one of the patents that is specifically referenced in the Accord and Satisfaction, Mr. Watt is going to be testifying about the Accord and

Satisfaction and about the rights that were granted under it, and this is one of the patents that was the subject of that.

It is the 120 -- EP 121 patent. It issues off the same family as the patents-in-suit, part of the same file history --

THE COURT: Is it incorporated by reference in the document that you had translated? I mean, how is it related back? Because there's a dispute here as to whether what's been translated is exactly the same thing.

MR. PRITIKIN: Yes.

THE COURT: How would I come to some sort of conclusion on that?

MR. PRITIKIN: So the original application that was filed was filed, as your Honor knows, it was filed in German, in Europe back in 1990. That original application became the specification of this European 121 patent. It also became the specification of the U.S. patents-in-suit.

9:34A The original application that was filed in German was translated by Sandoz. They provided a certified translation of that original application, which is the specification of this patent.

THE COURT: Is there any way to know if there were any amendments though?

MR. PRITIKIN: Well, one could look at the file history to see if there are any but --

THE COURT: Has anyone done that?

MR. PRITIKIN: They're familiar with the file history. They've been studying it for years. There's no indication that there's anything of any consequence that happened in the European Patent Office or any amendments there after August of 1990, so there's no basis for raising a question as to whether it's the same.

THE COURT: Ms. Rurka.

MR. RURKA: Your Honor, they produced this document to us and we're supposed to anticipate that they were going to bring a brand new document into the case last week, Wednesday, and scour through the file history that's in German to figure out whether or not any amendments to the specification were being made? That's what Mr. Pritikin is arguing today, when all they had to do was provide a certified translated copy to prove that it's the same specification.

9:35A THE COURT: Can we get a certified translated copy? How difficult would that be?

MR. PRITIKIN: So, I'm told that, in fact, we provided the certified translation, not Sandoz. So I stand corrected. But they've had that forever, the translation of the relationship application.

THE COURT: But just so that this is on solid footing, how difficult is it then to get a certified translated copy of this?

MR. PRITIKIN: I assume it can be done. I mean --

THE COURT: Why don't we just do that so then there's no dispute? And I understand what you're saying, that the previous document was already translated and there's no indication of any amendments and so on. But to the extent there's any dispute about any amendments, if it were certified as a prosecutor translation we could just move on from it.

MR. PRITIKIN: It can be done. I'm told it would take about a week to get a certified translation of it.

THE COURT: Well --

MR. PRITIKIN: Let me make this suggestion, your Honor.

THE COURT: Yes.

MR. PRITIKIN: What I would propose is that we go ahead, we proceed, we conduct the examination, we can get a certified translation of it, we'll provide it to the other side. If they think there's some basis in there for coming back or some question or discrepancy that's been raised, we can figure out at that point what we would need to do. But I hate to hold up the whole proceedings for a week while we do that.

9:36A THE COURT: Although if they mentioned it last week. A certified copy could have been obtained last week as opposed to being discussed today --

MR. PRITIKIN: For the same reason, I explained this morning, we saw no reason to do that because it is the same, it

is the same specification that led to it.

THE COURT: I understand your position. But Defendant's position is they would have to go through the whole file history to determine whether there's an amendment. And your position is, they should know that. They're here arguing this case, they should know it. But at the same point if we're going to rely on that a document -- it sounds like really the only thing that's in English is the claim, so that sounds fine, you can address the claim. To the extent you're going to dive deep into the rest of the document, it sounds like there's a challenge.

MR. PRITIKIN: And I think the questions I'm going to be asking about the claims are clear on the face of the claims, your Honor. If they think there's some reason to go into the specification or a need to do that, certainly they can tell us then.

THE COURT: So I'm going to allow it in now conditionally. You're going to get us a certified copy and present it to the Defendants. If there's any issue after we conclude on this, you may contact the Court and let us know and we'll deal with it if we need some sort of further development of the testimony.

Thank you.

MR. PRITIKIN: That's fine. Thank you, your Honor.

9:37A THE COURT: Thank you. All right. What's next?

MR. HAEFNER: So in anticipation of Dr. Arora later today, your Honor, in Sandoz's case, this is a deposition clip. There is a dispute about a document that is included in the clip. This is Dr. Arora's resume which she specifically testified at her deposition she created for the purpose of getting a job. She was not employed by Amgen --

THE COURT: I'm sorry. There's a dispute over her resume?

MR. HAEFNER: They want to move it into evidence, your Honor.

THE COURT: Okay.

MR. HAEFNER: And it's hearsay. And at the deposition she, in fact, confirmed that she created it for the purosess of getting a job. It doesn't have any indicia of reliability, and we don't want that exhibit to come in, nor do we want the related testimony to come in.

THE COURT: She could go through each thing and identify what she's done, no? And say, yes, I worked here during this period of time; yes, I wrote this article; I did the following research. She would be able to do that. No?

9:38A MR. HAEFNER: I don't believe so, your Honor. I mean, it is an out-of-court statement offered to prove the truth of the matter asserted. It's not her statements as -- it's not statements about what she did at Amgen in the context of being a current employee at Amgen. It's a statement referenced to a

resume, a resume which is not admissible for the purpose of examining the parts of the resume that are puffery and then using that to construct an argument that they should be taken at face value for the truth of the matter asserted.

And that's what we have a problem with, your Honor.

THE COURT: Okay.

Counsel.

MS. RENE: So, your Honor, the Plaintiffs' objections to this include both testimony and the actual CV itself.

So, during her deposition, Dr. Arora was asked about her CV and explained various entries in her CV, just as your Honor suggested one might do doing a deposition, and those are the portions that's Plaintiffs are objecting to. And just to provide the adequate context of who Dr. Arora is and why this is relevant. Dr. Arora submitted a declaration to the PTO during the prosecution of the patents-in-suit regarding the unexpected results relating to effector functions of CDC and ADCC.

That declaration was relied on by Dr. Greene, who was Plaintiffs' witness during his testimony. And the testimony at issue that they're objecting to specifically relates to her CV and her description and her testimony about her role as a scientific liaison for the legal team at Amgen. Specifically, she testified consistent with her CV that she was a scientific liaison for legal teams, to tackle intellectual property

related matters for marketing drugs, pipeline, and emerging technologies, help formulate strategy for stronger IP, innovator molecules, and defensive strategy for biosimilars. A key impact was for Enbrel as setting patent protection for another 16 years past its 2012 expiration date.

So that portion of her CV was discussed during her testimony. She explained it, she explained her role at Amgen, including her role in the scientific studies relating to the declaration and the purposes of the declaration.

THE COURT: Okay. Is she coming in live, or is this --

MS. RENE: No, this is a deposition designation.

And also Plaintiffs at her deposition did examine her on her CV, including the purposes for her creating the CV which -- to get a job, which is why most people create those CVs, and they have designated that testimony, so it will be played as well.

So from our perspective these things are not hearsay. We are not offering it for the truth of the matter asserted, we're offering it it to provide context for her testimony. It's relevant to her testimony. She's the one who did the testing at Amgen and the Plaintiffs relied on --

9:42A THE COURT: Why wouldn't the testimony be sufficient on its own without the CV?

MS. RENE: They're also objecting to -- the testimony

might very well be sufficient on its own, but they're also objecting to that testimony.

THE COURT: What's the objection to the testimony?

MR. HAEFNER: Two things, your Honor. There's no objection to the testimony about her work on the declaration, about her interaction with the Patent Office. The concern is that then when one turns to the CV created for the purposes of getting a job and obviously glossed in a manner that would make her an attractive candidate, one sees this language which was read to you about how she was, you know, assisted in extended patent life, et cetera, et cetera.

You know, this is not what her job was at Amgen. She testifies about in the designations about what her job was, what she did on a daily basis. There's no objection to that. The objection is to the spin on, let's use your CV to now create this narrative, a CV which is hearsay to create this false setting.

9:43A THE COURT: But during the clip I imagine you cross it, don't you?

MR. HAEFNER: There is testimony, your Honor, which I'm not positive got into the final clip, so there does have to be a discussion off line about these lines. But, yes, there is testimony about how the CV is specifically for the purpose of obtaining a job.

THE COURT: Okay. Well, this is what I'm going to do

on this: I'm going to allow it so I can listen to it and see how it fits into the testimony. But I am very cognizant of the objection, and I'm going to take a further look at it. So it's conditionly admitted at this point, and I may allow it in or may not allow it in depending upon how things go. All right. Thank you.

MS. RENE: May I just make one more note on that, your Honor?

THE COURT: Yes.

MS. RENE: Thank you. I appreciate it.

As I stated before, we don't believe that it's being offered for the truth of the matter as the resulted. But even if it was offered for truth of the matter asserted we believe that it falls within -- it's admissible subject to Federal Rule of Evidence 807 under the residual exception to the rule against hearsay. Dr. Arora testified that the document is indeed her curriculum vitae. She reflected circumstantial guarantees of trustworthiness, and as your Honor will hear from the clip, she did explain if fully. So I just wanted to note if for the record as well.

9:44A THE COURT: I'm curious to see how the testimony stands on its own without the resume. I'm not certain at this point because I'm listening in advance of hearing it, how intertwined it actually is. Have you folks taken another look at this?

MR. HAEFNER: Your Honor, I don't believe, your Honor, that the that portions of the deposition which deal with the facts of the case are intertwined with this discussion of her CV and the gloss she had put on on it.

And as to the 403 -- or excuse me -- the 807 --

THE COURT: 807.

MR. HAEFNER: -- exception, she admits in the deposition itself that its for the purposes of getting a job. And as anyone who has made a CV or resume knows, that is not an indicia of reliability.

(Laughter.)

MS. RENE: I don't know if I would agree with that.

THE COURT: All right. Let's move on from that.

MS. RENE: Thank you.

THE COURT: What's next?

MR. HAEFNER: There's nothing at the moment, your Honor. There's a brewing discussion of documents related to Dr. McDuff, but all or portions of it may be worked out, and so we're just going to hold --

9:45A THE COURT: So hold on that if you're still having a conversation regarding it, that's fine.

Anything else?

MR. HAEFNER: Let me --

THE COURT: Look through your notes.

MR. HAEFNER: That is it, your Honor.

THE COURT: Sounds good. Anything else?

MS. RENE: No, that's it, your Honor. Thank you so much.

THE COURT: Thank you very much. Let's move on then.

MR. RURKA: Your Honor, we call Professor Arne Skerra.

THE COURT: Thank you very much.

You may come forward.

MR. RURKA: I believe you have the binders.

THE COURT: Good morning, sir. You may come forward. Thank you.

We'll have the witness sworn in.

MR. RURKA: May I approach?

THE COURT: Certainly.

How are you, good morning?

DR. SKERRA: Good morning.

A R N E S K E R R A, called as a witness, having been first duly sworn, is examined and testifies as follows:

THE DEPUTY CLERK: Please be seated. State your name for the record.

THE WITNESS: My name is Arne Skerra.

9:46A THE COURT: Try it again. You can speak right in. Just say "test."

DIRECT EXAMINATION

BY MR. RURKA:
Q Good morning, Professor.
A Good morning.
Q Could you please state your name for the record?
A Arne Skerra.
Q And, Professor Skerra, what is your current occupation?
A I'm a full Professor at the Technical University of Munich.
Q And what is the Technical University of Munich?
A Now in Germany a technical university is a kind of university which is devoted to the natural sciences and engineering as opposed to philosophical sciences, and among the German technical universities, I think the Technical University of Munich is one of the leading universities.
Q Thank you.
Can you provide, describe your work at the Technical University of Immunology?
9:47A A Yes. I'm a professor of biological chemistry, and I teach biological chemistry in various flavors. That means I hold my chemistry courses at the undergraduate level, and more specifically, I teach protein biochemistry at the masters level and graduate level. And in addition, I work in research, so my laboratory hosts approximately 25 co-workers, and we are working on several topics in the area of protein design and protein biochemistry.
Q And, Doctor, is this your first time testifying at trial?

A Yes.
Q Okay. And, generally, you're providing expert testimony today. Can you give a general overview of the topic you're your testimony is directed to?
A I was asked to provide my opinion about the way how etanercept interacts or binds to TNF.
Q Okay. Did you bring your CV to court today?
A Yes, I did.
9:48A Q Can we please turn to DTX-1249.
A That's my CV, yes, so the first page of it.
Q Did you prepare some slides to help the Court today?
A Yes, I did.
Q All right. Why don't we put them on the slides for that.
MS. RURKA: So let's go to DTX-3001. And can you describe your education for the Court, Doctor?
A Yes, I accomplished chemical studies at the Technical University of Darmstadt and completed my studies with a degree of a chemical engineer, and this was at the end of '85; and in the beginning of '86, I moved to the Ludwig Maximilians University of Germany -- of Munich -- sorry -- which is the other big immunology university, and there I did my Ph.D work, and I worked on the topic of "Functional Expression of Antibody Fragments in E.coli," which is a common laboratory material; and I finished my Ph.D studies with the German equivalent degree of the US Ph.D, at the end of '89.

9:50A Q What was the subject matter of your Ph.D research, Doctor?
A As I mentioned, I worked on antibodies and antibody fragments, the way how they can be produced in the laboratory bacteria, how they can be purified and their binding can be investigated.
Q Okay. Let's turn to DTX-3002. And can you describe what you did after completing your graduate research?
A Yes, certainly. So in the beginning of the year 1990, I went to England and to the Medical Research Council Laboratory of Molecular Biology in Cambridge and joined Dr. Milstein's department; and one year later I received a position as a group leader back in Germany at the Max-Planch Institute for Biophysics in Frankfurt; and in '94, I received my first appointment as an Associate Professor of Protein Chemistry at the Technical University of Darmstadt; and finally, in '98, I received my present appointment, that is the full Professorship in Biological Chemistry at the Technical University of Munich.
9:51A Q How long have been you be conducting research in the field of biological chemistry, Doctor?
A I think that kind of research started early in my Ph.D thesis, so it is now more than 30 years.
Q Have you published articles over the course of your career?
A I have. I would say more than 200 articles, both basic research articles or original research articles, and reviews and book chapters.

Q Let's go to DDX-3003. Have you been a member, held leadership positions within your field?
A Yes. I have been a member of the German Chemical Society for more than 30 years, and there I served as an elected board member, and for a couple of years also as a Chairman of their division called Biochemistry. Also I have been a member of the German Society of Biochemistry and Molecular Biology, GBM, and there I have served as a Chairman of their study group, Protein engineering And Design.

Apart from my scientific interests, I was also interested in translating my research into practical applications, and over the years I have co-founded two companies, two biotech companies with the goal of developing biopharmaceutical drugs. And the first one is Pieris, which by now is called Pieris Pharmaceuticals, Inc., in fact, it's listed on the NASDAQ companies the last couple of years, and the other companies is XL-Protein, GmbH.

9:52A Q Doctor, are you the member of any editorial boards?
A Yes. I have been serving on the editorial board for the editorial advisory board of several international scientific journals, among those, the Journal of Molecular Biology; the journal called Protein Engineering Design and Selection, and some others.
Q Okay. And have you received any professional honors or awards?

A Yes. Over the years I was lucky to receive a couple of awards. Among those, for example, is my election as a full member to the German Academy of Science and Engineering; I also received some medals and prizes, both in Germany, for example, the Heinz Maier-Leibnix medal, but also internationally. So, for example, I won the Universal Biotech Prize of Innovation in Paris, France; and also in the U.S. I led a team that received the -- or that was awarded as grand prize winner in the International Genetically Engineered Machines competition which took place in Cambridge, Massachusetts.

9:53A MR. RURKA: Your Honor, defendants would proffer Dr. Skerra as an expert in the field of biochemistry, protein chemistry and chemistry -- I'm sorry -- protein biochemistry and chemistry.

THE COURT: Thank you.

Any objection?

MR. WINTERS: There will be some cross-examination in this area, but no objection to his admission as so moved, your Honor.

THE COURT: Thank you so much.

So he is deemed to be an expert in these areas and he may so testify.

MS. RURKA: Thank you, your Honor.

THE COURT: Thank you.

MS. RURKA: Let's turn to DTX-3005.

Q And can you just offer a general road map of the opinions you'll be offering today?
A Yes. As I already mentioned, I was asked to provide my opinion on the properties of etanercept and their interaction or binding to TNF. The first opinion is on the topic: Etanercept's strong TNF-binding is not unexpected;

The second opinion is: Etanercept's lack of aggregation is not unexpected; and

Third, etanercept's role in CDC and ADCC is not unexpected.

9:54A Q Okay. Let's turn to DTX-3006, and talk about the perspective that you applied when you did your analysis.

You're aware that Dr. Blobel offered an opinion on who is a person of skill in the art?
A Yes, I do.
Q Okay. And DDX-3006, you understand this is the definition he applied?
A Yes. Dr. Blobel expected from a person of ordinary skill in the art, he had an MD or Ph.D in biology, molecular biology, biochemistry, or chemistry or a similar field.

In fact, my Ph.D is in the field of biochemistry.

And this person should have one to two years of experience in the field of immunology or molecular immunology, and some other techniques which I -- at least part of them I was well aware at the time.

Q Okay. And did you conduct -- did you have one to two years of experience in the field before the priority date?
A Yes. So in particular, both during my Ph.D thesis and at the time thereafter at Cambridge I worked on protein biochemistry, protein purification, I was familiar with immunological assays, and I was experienced in cloning and expression of DNA.
9:56A Q So, in your opinion, are you qualified as a person of ordinary skill in the art as of August 31st, 1990?
A Yes, I believe so.
Q Okay. Let's turn to DDX-3007, and we'll start with your first opinion that: Etanercept's strong TNF-binding is not unexpected.
And before we get into the meat of your testimony, why don't we talk about some concepts and terms that will be relevant for your testimony.
So let's go to DDX-3008. And, Doctor, can you just talk through what a TNF trimer is and what that means?
A TNF is a cytokine. That means it's a signaling protein in the immune system, and its structure was elucidated by Eck and Sprang and shown in the publication of '89. And he received one picture from the publication. And here we see a kind of trace which is meant to illustrate the chain of amino acids that forms this protein.
And it's a bit difficult to see here on this slide

but, in fact, there are three different traces: One shown in red, one in light blue, and one in light green. And this indicates that TNF is a trimer of three identical chains of amino acids.

9:57A Now, for the following of my talk I will use a more simplified representation which is shown to the right where we see, let's say, three egg-shaped objects. These should stand for the polypeptide chains, and I will also refer to them as the three subunits of the TNF trimer. And all three subunits are mutually identical.

Q By "mutually identical," what does that mean for TNF-binding?

A It means the expectation is that there are three binding sites because each subunit offers one binding site for the receptor.

MS. RURKA: And just for the record, the Eck and Sprang article, that's JTX-26 at page 4. That's where the image comes from.

Q Okay. Let's turn to DDX-3009.

And why don't we talk through what you're showing here. We have two different figures. And can you explain what those are?

A Yes. These figures are schematic representations of the molecular structure of etanercept. So on the left we see here in green -- so, first of all, etanercept is a dimeric protein

so it is composed of two identical chains of amino acids. And in the upper part, the green moiety, this represents the extracellular portion of the TNF receptor; the dark blue moiety at the bottom, that's the CH2 and CH3 regions or domains of an immunoglobulin; and in the middle, the light blue part, that's the hinge region which also has cysteine residues and disulfide bridges.

9:59A Now, on the right we see a slightly more detailed picture as it was used by expert Dr. Greene, so in principle it looks the same. It has a bit more granularity on the extracellular portion of the TNF receptor, which is also known as p75 receptor. And here we actually see what was known from the literature, that this extracellular region forms four domains which are linked by more or less flexible linkers.

At the time it was not known where the binding site for TNF is, it was not clear whether it's on the tip of this receptor moiety or maybe on the side of one of its domains. But for the protein biochemist such a picture makes already clear that this TNF receptor has a certain degree of flexibility so it would allow the TNF to approach in several ways.

Q Okay. And by the "domains," those are depicted in Dr. Greene's pictures as the blobs?

10:00A A Yes.

Q Is that accurate?

And connected by little amino acid chains. Is that right?
A Stretches of amino acids which probably are flexible.
Q Okay.
A But for the following, I will refer for simplicity to the left picture.
Q And, Doctor, before we continue, you prepared an expert report in this case. Is that right?
A Yes.
Q And you were asked to make an assumption about what the TNF receptor portion of etanercept looks like. Is that right?
A Yes.
Q Okay. And you understood at the time that the full TNF receptor extracellular region has 235 amino acids. Is that right?
A Yes.
Q There was a typo in your expert report. Isn't that right?
MR. WINTERS: I'm sorry, your Honor. That's quite leading. There's a paragraph --
THE COURT: Rephrase it.
MR. RURKA: Yes.
10:01A Q What did your expert report state about the extracellular region of the TNF receptor in etanercept?
A I was -- there were two numbers given to me as a basis of my opinion. I believe it was 275 residues or 185 residues.

But the actual number did not really play a role for my opinion because it was so important for me to see that all these four domains are present in this extracellular portion.

So my assumption was that this was a biologically active extracellular region of a receptor, it has a certain structure, it has obviously the binding sites for TNF-alpha, and this is the situation under which I then imagined how such a soluble version, such a fusion protein of the TNF receptor, would interact with TNF.

Q Okay. Thank you, Doctor.

Let's go to DDX-3010. Have you reached an opinion about the expected binding in 1990, of what a person of skill in the art would have expected a molecule like etanercept, how they would have expected it to bind to TNF?

10:02A A Yes, that's actually my opinion. If I imagine, if what I know, or what I would have known at the time about the structure of etanercept on the one hand and the trimeric structure of TNF on the other, then I would have assumed or expected that etanercept would form this kind of one-to-one complex as I would call it, where each arm of etanercept, so each extracellular receptor, will bind to one subunit on TNF. That means two subunits of TNF occupied, the third subunit remains unoccupied except for certain circumstances which we may discuss later.

Q Okay. So let's turn to DDX-3011.

And what we have here, Doctor, is a slide from Dr. Naismith's presentation. Did you read Dr. Naismith's testimony?

A I have read that part of his testimony that refers to the topic here. I have seen the slide and the slide looks familiar to me.

10:03A Q Okay.

A Because this is a very generic illustration how in principle a biovalent binding protein -- and I don't think we see here already a distinction, whether this would be an antibody or it would be etanercept. It's a very general illustration how a biovalent binding protein could interact with a trimeric antigen like TNF.

Q So why don't we talk about the three modes. What is Mode 1?

A Yes. In Mode 1 we see that each arm, each binding arm of the binding protein binds to one subunit the TNF, and these are two separate TNF trimers. So this is called a monovalent binding because each arm binds to one TNF trimer independently of the other arm.

Q How about, Mode 2?

A Now, Mode 2, that would be called bivalent binding because we see that one arm, again, binds to one subunit of the TNF trimer, but the other arm of the molecule binds to a different subunit part of the same TNF trimer. So both particles, the

TNF and the binding protein, are connected by two bonds, and this is why we call it bivalent binding.

Q And how about Mode 3?

10:04A A Mode 3 is maybe a more simplified version of Mode 1, where just one arm of the bivalent binding protein binds to one subunit the TNF trimer.

Q Okay. So let's go to DD-3012 and talk about Mode 3 first. What is your opinion about Dr. Naismith's -- the role of binding Mode 3?

A Now, compared with Mode 1 and Mode 3 -- Mode 2, -- excuse me -- Mode 3 is, in my opinion, more kind of transient or intermediate state because this would be the first complex that is formed when the bivalent binding protein encounters the trimer TNF. Of course, naturally one arm would first bind to one subunit on the TNF trimer and we arrive at Mode 3.

But, in my opinion, the process doesn't stop here, because now the molecule has essentially two options how to react further. And one option would be to use its second arm. So the bivalent binding protein would use its second arm to engage with a second subunit on the same TNF trimer. So this would in the end lead to Mode Number 2; or alternatively, if there are additional copies of TNF present, then the same arm could potentially bind to another TNF trimer and then we arrive at Mode Number 1.

10:06A Q Between Mode Number 1 and Mode Number 2, which binding mode

would be preferred, or would be expected to be preferred?
A Now, in my opinion, Mode Number 2 would be strongly preferred, and this would be the default mode of binding.
Q Okay. Let's turn to DDX-3013 and talk about why Mode 2 would be preferred.
What we have up here is DTX-84, which is the Roitt textbook, Doctor. Is that right?
A Yes.
Q And this is on page 5. And can you talk to us about what Roitt terms us about bivalent binding and monovalent binding?
A Yes. So Dr. Ivan Roitt wrote a famous textbook on immunology which I also used during my Ph.D thesis and which I still have on my shelf today, and in his textbook he explains the so-called avidity effect, and he also explains the difference between avidity and another phenomenon called affinity. And affinity, that's, let's say, a simpler version.
10:07A Now, he says in the explanation of this table, which I will come to in a moment, his statement is: Multivalent binding between antibody and antigen (avidity or functional affinity) results in a considerable increase in stability as measured by the equilibrium constant, compared to simple monovalent binding (affinity or intrinsic affinity).
So that's a very fundamental statement which is illustrated in the table.
Q Okay. And so multivalent, is that the same as bivalent in

this context?
A Multivalent is the more general expression. Bivalent in principle, they are also binding like bivalent and so on. But bivalent is the simplest mode of multivalent binding.
Q And this textbook references antibodies. Does this table apply, or the concept of the affinity and avidity apply beyond antibodies?
10:08A A Of course this is a textbook on immunology so it focuses on antibodies and antibody-like molecules. And this is also why there's divisions at the top, at the top that are referred to antibodies. But the fundamental principle of avidity applies to any kind of bivalent binding protein.
Q So let's turn to DDX-3014, and take a look at Dr. Naismith's binding modes. And let's talk first talk about binding Mode 3.
Does Roitt have a column for what would represent binding Mode 3?
A Yes. Now, in this column, Dr. Roitt actually distinguishes four different cases, and I will now discuss the relevant cases here.
Column number two -- unfortunately, the battery is empty.
Q Oh.
10:09A (Batteries for laser pointer are handed up to Witness.)

MR. RURKA: Thank you, Mr. Haw.

Q Now, column number three in this table illustrates a situation where an antibody -- and this is this Y-shaped molecule or protein at the top -- interacts just with one of its two arms which are also known as FAB arms for the antigen binding fragment, which is shown here as a small particle. And this is essentially the same situation as illustrated in the Mode Number 3 which I discussed before. So here the bivalent binding protein interacts with one antigen particle, one TNF trimer.

10:11A And this table characterizes this situation as a normal affinity direction. And "affinity" means its strengths of binding. And it says the number of valence is 1, so it's multivalent binding, and it gives here a certain equilibrium constant which is arbitrarily chosen as 10 to the 4.

Q Okay. And I think you said "multivalent" binding. Did you mean "monovalent" binding?

A I'm sorry. I meant monovalent binding. So univalent, monovalent binding.

Q Let's take a look at Binding Mode 1. And what would Binding Mode 1, where would Binding Mode 1 fall in this chart?

A Mode 1 would fall into the same category. Because as I explained before, each arm of the bivalent binding protein independently interacts with one antigen particle -- here it would be the TNF trimer -- independently of the other arm. So

again we have a situation here which is characterized by the term "affinity," and it's characterized by the term "monovalent binding."

Q Okay. And so let's go to slide DDX-3015. And where does Mode 2 then fall within this chart?

10:12A A Now, Mode 2 is definitely a different mode of binding according to the classification by Dr. Roitt. Because here this situation resembles column number 4.

So here at the top we see an antibody that is now engaged with both of its arms. So both arms of the Y bind to an antigen, but these antigens are part of one particle. And here in the context of immunology, this looks more like a cell surface or maybe a virus surface. But the fundamental principle is here that the antigenic sides are part of one of the same particle. And this would also be possible -- sorry -- that would also be the situation for the three subunits of one TNF trimer.

So Mode 2 clearly corresponds to this column here on the table. And now we see that this kind of interaction is characterized by the term "avidity." So that's this special situation which is strongly favored.

And this can be seen from the value of the equilibrium constant which is now 10 to the 7. So simply dividing 10 to the 7 by 10 to the 4 means we have a so-called 1,000-fold advantage as a consequence of this monovalent over here,

bivalent binding. And that's the avidity effect.

10:13A Q Thank you, Doctor.

And do you have an analogy that kind of brings it down to laymen's terms?

A Now, in my understanding, this is a natural driving force for molecules. So there are certain driving forces in nature, yeah, which we cannot change as humans. And it's very similar like -- like a human person that also has some natural ways how to act.

So, for example, if I have seen now over the course, many of these paper boxes, big boxes with many paper in it and they have two handles on both sides. And if I as a person wanted to move such a box from one place to another, of course I would first use my first binding side one arm to grab one handle, and then I would feel the box is actually too heavy and I need my second arm, and I would take it to lift it up because this is a much stronger interaction, a much stronger binding, it gives me more grip on the box. And this is at least in my understanding a very similar way as molecules try to interact with their partners in the most intimate way.

10:14A Q Okay. Now, let's turn to Dr. Naismith's testimony on direct.

MR. RURKA: Mr. Haw, can we go to page 111, lines 14 through 25. And let's take this two at a time.

Q So, did you read this portion of Dr. Naismith's testimony,

Doctor?
A Yes, I did.
Q Okay. And he was asked on direct:
"As a matter of first principles, at the time of the patent, was there a particular mode that was thought to be more likely than the other?"
His answer was: "The first principles would indicate Mode 1 is much preferred because it has the least stereochemical restraint or conditions."
Doctor, do you agree with that testimony?
A I do not agree with the it, because I feel and it is my honest opinion that Mode Number 2 is the preferred mode.
Q Okay. Let's take a look at the next question:
"Would you mind telling me as if I were a sixth grader what that meant"?
And his answer was: "Just that this idea that three dimensional space in Mode 2 is really only one arrangement. So you have the molecule is prefigured in that arrangement, or is able to adopt it without paying too much of an energy penalty."
10:16A And what is your opinion about the energy penalty that Dr. Naismith is discussing?
A Now, first my opinion is that his answer is, let's say, a one-sided view. He only looks at the structure. But as a scientist one also has to keep in mind another general phenomenon that is entropy. And only if you consider both you

will come up with a meaningful interpretation. So I do not think that this energy penalty plays a major role here, and I can illustrate this in the next slide.

Q Let's go to DDX- 3016.

And can you explain what you're showing here?

A Yeah. Because when I saw Dr. Naismith's illustrations of Mode 2, illustration of Mode 2, I had the feeling that this kind of binding of the bivalent protein to this TNF trimer is overly complicated because it looks like arms are being crossed, and this is actually, for a molecule, this is indeed unnatural.

10:17A But the point is, what is neglected in this way of presentation is that the two arms of a molecule actually can much more rotate than the human arm, so they can actually rotate by 360 degrees, which I cannot do with my arms, but the molecule can do. And just by rotating and then turning, turning the bottom, this would be like half of a movement of a dancer. The whole situation relaxes, and we come up with something which I would call Mode 2B, and this looks now much more relaxed. And this kind of energy penalty which may certainly happen in Mode 2A is no longer present.

Q Can we turn to DDX-3017.

So can you summarize your opinion about the expectation of a person of skill in the art in 1990, about the favorite binding mode between a bivalent binding protein and

trimeric TNF?

10:18A A Yes. So in the end you have to distinguish now between Mode 1 and Mode 2. And as I explained, Mode 2 is strongly favored by this well-known avidity effect at the time. And that explains my preference, my strong preference or expectation of Mode Number 2.

Q Okay. And let's go then to etanercept, go to DDX-3018.

What would the expected binding mode be for a molecule like etanercept then?

A So far the pictures are kind of a generic nature for a kind of bivalent binding protein. Now we go back to the molecular structure of etanercept.

And here we have exactly the situation that allows this kind of bivalent binding because each arm of this extracellular receptor portion as part of etanercept can bind to a different subunit but on the same -- and that's the important thing -- on the same TNF trimer.

Q Okay. Let's go to DDX-3019.

10:19A And this is clipped from Dr. Naismith's direct presentation, his demonstratives. And Dr. Naismith opined that etanercept exhibits unexpected binding properties because it binds TNF 50 times tighter than the soluble receptor.

Which, Doctor, you understand that's just the p75 receptor by itself. Right?

A That's the p75 receptor just cleaved off its transmembrane

part, yes, that's what I understand, and it would be a monovalent binding protein.

Q And then he also opines that it neutralizes TNF. It's unexpected that TNF -- that etanercept neutralizes TNF 1,000 times better than the soluble receptor.

Do you agree with those opinions?

A No, I do not agree, and essentially for the same reasons which I explained before.

Q Okay. Let's go to DDX-3020.

A Because this avidity effect strongly indicates, or predicts actually, that it is not only the mode of binding which is preferred, that means this bivalent mode of binding, but also that we have this advantage of multivalence, as Dr. Roitt called it. And this is a 1,000-fold advantage as a general number, as a, let's say, average number I would say.

So it is easy. If a molecule is a bivalent binding protein can participate in this -- in this bivalent interaction with its antigen, with its trimeric TNF, then it's easy that this strengths of binding is 1,000-fold stronger compared with the soluble receptor.

And the soluble receptors is actually a situation that is already foreseen in Dr. Roitt's table. Because here we have just this monovalent portion of the TNF receptor, and this looks very much like just the binding arm of an antibody. So that would be this FAB fragment. And the FAB fragment can also

only interact with one antigen at the time. And clearly the FAB situation like the soluble receptor situation is only characterized by ordinary affinity which cannot take advantage of this beneficial effect.

10:21A Q Thank you, Doctor.

Let's move to your second opinion and let's go to DDX-3021.

And your second opinion is: Etanercept's lack of aggregation is not unexpected.

And let's go to DDX-3022 then.

You explained that the expected binding mode for etanercept would be Mode 2. And is there a relationship between that binding and aggregate formation, Doctor?

A Yes. And that's a simple matter of logic. Because when I formed the complex between etanercept and the TNF trimer, then both arms of etanercept are saturated, as we would say as scientists. That means they already are fully occupied with one and the same TNF trimer, and so there would be no tendency for additional interactions of etanercept.

Q Let's go to DDX-3023.

And can you explain more generally how that would preclude aggregation then?

A Yes. Now, if we have a solution where there are many copies of etanercept and the similar -- or also many copies of TNF, then all the etanercept molecules would tend, or strongly

tend to interact with one trimer each. And as there are no additional binding sites awakened on the etanercept molecule, no further cross-linking can take place. And without cross-links there is no aggregate formation.

10:22A Q Let's go to DDX-3024.

What does the prior art teach about Binding Mode 2 versus aggregation for a bivalent binding protein, with the trimer target?

A Yes. There's another famous publication which was well-known at the time, already before Roitt published his textbook, and this publication provided the rationale for finding, which was very known in the area of immunology, and as a, let's say, summary of both the experimental situation and the theory which was provided here by Drs. Crothers and Metzger. They made the following statement, they said:

"In situations where multisite adherence to a single particle and cross-linking of discrete particles are both possible, the former is predicted to predominate strongly.

10:23A Now, this is slightly complicated statement. What does it mean?

Multisite adherence to a single particle, that's exactly this Mode Number 2. That means bivalent interaction as shown here between the two arms of all binding protein with the three subunits of TNF. So that's the multisite adherence.

And opposed to that we have higher order aggregate

formation, or simple aggregate formation, that would be the cross-linking of these three particles. So particles would be TNF particles here. When they get cross-linked we form this higher order mass. And there is clear prediction or clear expectation, that the first mechanism. That means this Mode 2, this one-to-one, this complex formation, that is strongly preferred or predominates.

Q Okay. And, Doctor, would you call Mode 2 the default mode?

A Yes, that would be the default expectation for the informed scientist at the time.

10:24A Q So, Dr. Naismith presented some post-priority date results for anti-TNF antibodies like infliximab and adalimumab. You understand that. Right?

A Yes.

Q And infliximab, just for the record, is Remicade; adalimumab is Humira. Do you understand that, Doctor?

A Yes.

Q Were these data available before August 31st, 1990?

A No, they were published much later.

Q Okay. Let's turn to DDX-3025.

How did these -- let's just talk on the general level -- how did these studies of the behavior of adalimumab and infliximab fit in with a person of skill in the art's expectations with respect to binding -- bivalent binding proteins?

A Now, the left side of this slide illustrates a situation I have been talking about in regards to etanercept. That means etanercept as a bivalent protein would form this one-to-one complex by way of bivalent binding to the same TNF trimer. This is here an illustration of the generic mode, Mode Number 2 or generic illustration.

Etanercept picks up the bivalent mode of binding which is Mode Number 2 shown here in the generic way, and on the left shown in the representation as the etanercept molecule.

10:26A Now, fundamentally, without looking into the details of the structure, for an antibody one would actually assume the very similar mode of binding. That means also bivalent mode of binding. But as I have seen in this later publications, obviously this doesn't happen, so obviously antibodies show a different behavior. And so obviously they prefer Mode Number 1. And something else happens which I think is illustrated on the next slide.

Q Okay. Let's go to DDX-3026.

What happens if you bind.

A Yes, now --

Q I'm sorry, Doctor, let me finish the question.

What happens if they bind in Mode Number 1?

A Yes. This is actually the expectation that they bind in Mode Number 1. And this is a situation which was already foreseen, for example, in the Crothers and Metzger publication

as an exceptional case.

Now, what happens here is that, first of all, once again we go through Mode Number 3, so the FAB arm of the antibody would bind the TNF trimer, and here we arrive at Mode Number 3.

10:27A And now, fundamentally, the other arm of the antibody should have some molecular driving force, as we would call it, to another subunit on the TNF trimer. But now we come up with a problem which is specific for antibodies. Because the arms of the antibody are rather stiff and bulky. And the reason for that is, that each arm of an antibody is made of not only of one chain of amino acids, but two chains of amino acids. So we have the upper part of the heavy chain and the upper part of The light chain. The are associated. They come into in a very intimate way, and they make this FAB arm very bulky and stiff.

And now the antibody faces the problem that its second arm can actually not reach around in order to bind to another subunit the same trimer. So that's something which I would call, or which is known as steric hindrance, and this is actually something which would lead to a energetic penalty.

10:28A Now what's the solution?

The antibody watches out for another TNF trimer and gets its second binding site saturated with a different TNF molecule, and that would be Mode Number 1.

Q Doctor, how does that make these particular antibodies

different than etanercept?
A Now, the difference here is that in etanercept we have this extracellular region of the TNF receptor which is made only of one chain of amino acids with their domains and with their flexibility, but here we have each arm composed of this double chain of amino acids which makes it much more bulky and stiff.
Q Let's turn to DDX-3027.
So what would the consequence of the monovalent binding of the anti-TNF antibodies be?
A Now, looking at the TNF trimer, from their perspective it means that only one subunit is bound to the antibody. So two subunits are awakened for additional interactions. That means binding to other antibodies.
And this is what can happen, and this is also a well-known phenomenon in immunology, that under some circumstances additional antibodies get bound with one arm and the other arm of the second antibody would bind to another TNF trimer.
So, in the end we come up with a situation where all these molecules get cross-linked, and this is now what we call a higher order aggregate or just simply an aggregate, and this can easily consist of several thousand or even more molecules.
10:30A Q Would that sort of aggregation be expected from etanercept then, or --
A Under these circumstances that's actually -- that's

absolutely my expectation.
Q I'm sorry.
A That's my expectation.
Q Would these sort of aggregates form -- would you expect these aggregates to form with etanercept?
A Yes, I would -- sorry, not with etanercept. Sorry.
Q Okay.
A So far I was talking about the antibodies. Now let's come back to etanercept.
Q Let's talk about etanercept.
What sort of --
A Now, we have to be here honest and clear about the situation of TNF. And in etanercept we also have one but only one subunit that is unoccupied.
So, of course, we can imagine a situation where there is excess amount of etanercept present, and then such additional etanercept molecules can bind to the third binding site. But this -- by logic this can only lead to two kinds of complexes, the one-to-one complex that would be the three-to-two complex shown here in the middle or the two-to-one complex shown to the right. But these are the highest complexes we can ever expect from etanercept based on this Mode 1 binding -- Mode 2 binding.
10:31A Q So let's go to DDX-3029.
And again, we have Dr. Naismith's slide up here or a

variation of his slide where he says: "Etanercept exhibits unexpected binding properties because it tends not to cause aggregations like antibodies."

Do you agree with that opinion?

A No, I do not agree with that. Because as part of my -- of this default mode of binding between etanercept and TNF it should not cause aggregation.

Q Actually, could we go back to DDX-3028.

Do you know whether or not this three-to-two or two-to-one binding would be enough to cause effector functions, Doctor?

A Not in my understanding, because it was -- it is known it was generally known in the field that in order to elicit effector functions like CDC or ADCC, we need much larger complexes with thousands of molecules in it. But here this is at most three molecules.

10:32A Q And is that understanding based on Dr. Greene's testimony?

A Yes, and also on my general knowledge. But I fully agree with expert Dr. Greene.

MS. RURKA: Okay. So, let's turn to DDX-3030.

Q And I'm sorry for that aside.

Dr. Naismith also testified that the Capon 1989 paper that's JTX-58 at page 2 demonstrates that a bivalent molecule like Dr. Capon's CD4 molecules, you would expect some agglutination with these types of bivalent fusion proteins. Do

you agree with that?
A No, I do not agree with that. And in order to understand that, we have to keep in mind it's not only the properties of the bivalent binding protein, it's also the properties of this antigen, the green blobs which are here. And it was well-known that in the way how gp120, the antigen used in this study, how it was applied, the gp120 was just in a monomeric state, not like a trimer like TNF. So it was only monomeric gp120.
And here it was absorbed through on red blood cells. And under such circumstances the bivalent binding protein has no other choice than binding according to Mode Number 1, that means with each arm grabging a different gp120 molecule on a different red blood cell.
10:34A Q And can we go to DDX-3033, and let's talk about Dr. Kohno.
You understand Dr. Naismith cited Dr. Kohno's work from 2007, again postdating the priority date?
A Yes. This was a very interesting study on the biophysical characterization of the way how antibodies on the one hand or etanercept on the other would interact or do interact with the TNF trimer.
Q. So, Doctor, before we get into that, you understand Dr. Kohno -- this is PTX-140 at pages 2 and 3 -- and do you understand Dr. Kohno was testing, again, adalimumab and infliximab against etanercept? Right?
A Yes, that's what I understand.

Q Okay. So what sort of results did Dr. Kohno find?
A Yes. Now, Kohno and colleagues, they used a method which is well-known, it's the size exclusion chromatography, and this is a way that allows us to study the size of particles that form in solution.

And let me start with the simpler result here which is actually shown for etanercept on the right. Let's first have a look at this red curve. And here we see something which we call a peak. And this peaks -- this peak corresponds to etanercept itself. So this is the position where this peak is on the X axis is an indicator of the size of etanercept.

10:36A And the blue curve, that's the result of a mixture of etanercept with the TNF trimer. And here we see that the peaks shift to the left. And the more to the left they shift, the larger is the molecular size. And this can actually be quantitated using some molecular size standards, this is what the colleagues did here, and then from the size it can be judged, what is the composition of this molecular species.

And here they conclude, we have actually two species, one is the two-to-one complex between etanercept and the TNF trimer, and the other one is the one-to-one complex, even though, not annotated here.

Okay. Now we go to the experiments with the two antibodies. Adalimumab is shown on the left and infliximab on the lower right of the left side of this slide. Again, we see

in the -- in some curves we see the individual components. That means before they are getting mixed. And again this gives peaks on the right side of these chromatograms which nicely correspond to the isolated antibodies. But the mixture shows a totally different appearance, so there are no peaks in the middle, we only see peaks to the left, and peaks to the very left means they must be very large.

So obviously there are several species. But the highest peak we see here for the aggregate, and this is indicated by the labels used by the colleagues of Kohno and co-workers. They say on the left side are the adalimumab TNF and infliximab in brackets "n times." And "n times" means there are uncounted numbers of both molecules present in this kind of particle.

So these are these typically -- these typical high order complexes with thousands of molecules in it, and very similarly for infliximab in the middle graph.

10:38A Q Thank you Doctor.

MR. RURKA: So let's go to DDX-3034.

Q And you understand that Dr. Kohno also tested, according to Dr. Greene, Dr. Kohno also tested these three molecules in Ouchterlony assay. Correct?

A Yes. The Ouchterlony assay, that's a classic biological assay. And here we can also, if present, we can detect aggregates when two molecular species encounter each other; so

TNF and then either one of the antibodies or etanercept.

And surprisingly, they found that such aggregates which are seen here so-called precipitation lines form between TNF and the antibodies. And this is actually what they state in their discussion: "The mAbs typically do not form precipitable complexes in these types of assays."

So that is the formation of aggregates between adalimumab an dTNF or infliximab and TNF was not expected from this site. They showed these antibodies showed the unexpected properties.

10:39A Q Okay. So when it says, "the mAbs"; mAbs, that's the antibodies?

A Monoclonal antibodies like adalimumab or infliximab.

Q Thank you, Doctor.

Let's go to slide DDX-3035, and we'll talk about your final opinion: Etanercept's role in CDC and ADCC is not unexpected.

And you understand that Dr. Greene -- I think earlier we talked about this -- that Dr. Greene testified that aggregation is required in order to elicit CDC and ADCC?

A Yes, I'm absolutely on the same page with him.

MS. RURKA: Let's go to DDX-3036.

Q What would be a person of skill in the art's expectations in 1990, with respect to ADCC or CDC activity of a bivalent molecule like etanercept in the presence of trimeric TNF?

A To my understanding the primary target of etanercept is the soluble trimeric TNF. And as I explained before, there I expect this one-to-one complex formation according to Mode Number 2. That means there would be no aggregate. And if there's an aggregate, there would be no CDC and no ADCC, and that's my expectation.

10:40A Q And on the left side of your slide you ever transitory membrane-bound TNF. Could you just explain what you mean by that?

A Yes. This shows essentially the way, how the TNF is produced in the body, and there's a so-called precursor, that means an initial stage of this protein, which is first made as a membrane-bound version, and only after cleavage of the part which I would call membrane anchor, only then the TNF, the soluble TNF is released into a solution, that means into the body fluids. And this release is mediated by enzymes, by so-called proteinases, which are very efficient in cleaving this TNF from the membrane anchor.

Q Let's go to PTX-30 in your book. This is a 2009 publication by Dr. Arora.

Have you reviewed this?

A Yes.

Q And do you understand that Dr. Greene relied on this and that the applicants relied on this in the Patent Office, or these kinds of studies in the Patent Office. Is that right?

10:41A A That's what I have seen, yes.
Q Okay. And again, this post-dates the priority date. Is that right, Doctor?
A This is from the year 2009.
Q Are you aware of any prior art testing regarding the CDC and ADCC activity of any anti-TNF antibody before August of 1990?
A No, I haven't seen such a study.
MS. RURKA: Okay. Let's go to DDX-3037.
Q And this is a call-out of part of Dr. Arora's paper. Can you explain for the Court what the experimental setting was used in Dr. Arora's studies?
A Yes. Arora and colleagues, they were interested in CDC and ADCC functions of TNF-binding proteins of antibodies in etanercept. And of course, in order to investigate CDC and ADCC, we need to have a cell-based assay. Because the phenomenon in the end is cytotoxicity, that means cell toxicity. We can only observe this if we work with cells.
10:43A And in order to study this, they created a so-called experimental system. And here they engineered cells to express a stable form of TNF in its membrane-bound state. That means the protein in the TNF trimer stays bound to the cell surface of these cells. And in order to achieve this, they produced a mutant protein. And in this study I believe they deleted 12 amino acids from the linker between the transmembrane region or

this membrane anchor and the actual TNF trimer. And in this way there's no cleavage site for the proteinase accessible, and apparently this leads to stably membrane-fixed TNF.

Q Did the results here say anything about how etanercept would work on soluble TNF or non membrane-bound TNF?

10:44A A I mean, there are some studies, but those studies performed with the mutated cell line only relate to the membrane-bound form of TNF.

Q Let's go to DDX-3038.

And because of the way this study was conducted, did the authors note any limitation of their results?

A Yes, of course, because these are artificially engineered cells with a foreign gene. That means the mutated gene inserted into the cells. This often leads to a phenomenon we call "over-expression," and this was actually noted by the authors in the discussion of their study when they say: "It should be noted, however, that the level of mTNF..." -- which would be the membrane-bound form -- "...expression on those MT-3 cells may reach supraphysiologic levels, representing a potential limitation of the functional studies."

That means it is not clear whether -- it's actually doubtful whether the number of membrane-bound TNF on those engineered cells reflects the physiological situation in the patient.

10:45A MR. RURKA: Okay. And this for the record is PTX-130

at page 6.

Let's go to DDX-3039.

Q I think we just mentioned earlier that Dr. Arora submitted a Declaration to the Patent Office in support of patentability of the patents-in-suit.

Do you understand that. Right, Doctor?

A Yes.

MR. RURKA: Okay. And I believe that's PTX-6.459.

Q We have up here on the screen page 2. And what experimental study did Dr. Arora use for the results she submitted to the Patent Office?

A Now, I have seen this report, and to the extent that I understand it or I see the experimental data, these are identical with the scientific publication I was just talking about.

Q Okay. Dr. Greene on his direct also mentioned another article by Dr. Mitoma. Do you recall that?

A Yes.

Q That was published in 2008. Correct?

A Yes, and the year before it was actually quoted in Arora's publication.

Q Okay. That's DTX-213.

Can you take a look at that in your binder and identify it.

10:46A A Please give me a moment.

Yes, it's in my binder.
Q And what is this --
A This publication is again about a comparison among infliximab, etanercept, and adalimumab with regard to ADCC and CDC.
Q Did you rely on this in forming your opinions in the case, Doctor?
A Yes.
Q Let's turn to DDX- 3040. First we'll take a look at the "Materials and Methods" section of the Mitoma paper. And this at page 2 of DTX-213.
And what sort of study conditions did Dr. Mitoma use?
10:47A A These also used a very similar approach but with differences in the detail. Again, they tried to prevent this TNF cleavage from the cell membrane by using or by engineering a mutated cell line. But in this case they didn't delete a stretch of amino acids but they replaced two amino acids in this linker region between the membrane anchor and the TNF trimer part.
But this had the same effect. That means the proteinase could no longer cleave off the soluble TNF from the cell membrane.
Q And if we go to DDX-3041, this is a call-out of DTX-213 at page 8.
Did Dr. Mitoma note any limitation of his results?

A Yes. Again, he's also was aware of the limitations of their experimental system, and they again -- or similarly they stated that in their discussion when saying, considering that our assay system utilizes a human T cell line with accumulated transmembrane TNF-alpha expression, our study is not without its limitations.

10:48A So again, the question is: How well does this translate to the physiologic situation in the patient.

Q And let's turn to DDX-3042 finally.

What results did Arora, Dr. Arora and Dr. Mitoma each present with respect to ADCC?

A Now, their findings are actually mixed because Mitoma and colleagues on the one hand, they saw that had ADCC activities were almost equal among those three agents, which means infliximab, adalimumab and etanercept; but, on the other hand, Arora and colleagues, they conclude that infliximab and adalimumab induced ADCC much more strongly than etanercept.

Q So those results conflict, Doctor?

A Yeah. So, it means for me that almost 20 years after the relevant date on which I was asked to provide my opinion, it was still not clear which role ADCC plays.

Q Thank you.

10:49A MR. RURKA: No further questions.

THE COURT: Thank you. Do you want to take a few minutes?

MR. WINTERS: Just a brief break.
THE COURT: Let's take ten minutes. You may step down. Thank you.
(Witness temporarily excused.)
11:03A (Proceedings resume.)

A R N E S K E R R A, resumes, testifies further as follows:

THE DEPUTY CLERK: All rise.
THE COURT: Please be seated. Thank you.
11:07A Any new demonstratives, or just the binders?
MR. WINTERS: Just the binder, your Honor.
THE COURT: Thank you. We're ready.
Go right ahead.
MR. WINTERS: Thank you,

DIRECT EXAMINATION

BY MR. WINTERS:
Q Good morning, Dr. Skerra.
MR. WINTERS: Could we have PDX-9.46 up, please.
Q Before we do that, would you agree, Dr. Skerra, that bivalent proteins are not, in fact, mirror images of each other? Is that correct?
11:09A A Yes.
Q And that was known at the time. Correct?
A Yes.

Q And, in fact, proteins have a directionality to them. Correct?
A Yes.
Q And that was known at the time?
A Yes.
Q And, in fact, scientists refer to proteins as having a handedness. Yes?
A Yes.
Q And they refer to proteins as having a left-handedness. Correct?
A Actually the handedness happens on the level of amino acids. And if we talk about L amino acids, "L" stands for left, yes.
Q And so the depiction we have up here of the bivalent protein with a left-hand -- this is PDX-9.46 -- dealing with the left-hand with the palm out and then a left-hand with the palm in, although it's a cartoon, as you scientists would say, that's technically accurate in terms of the way the molecule is constructed. Right? It spins about on an axis rather than being a mirror image of each other?
11:10A A Yeah. We call it a two-fold rotation axis, that's true. The two parts of any bivalent protein are related by 100 degrees rotation.
Q Okay. And so the hands Dr. Naismith has put up there, although it's simplified, that's technically accurate with

respect to a bivalent protein. Yes?
A I imagine.
Q Okay. Why don't we take a look, please, if we could at the 37slides you just presented to the Court.
MR. WINTERS: And if we could put up, Bill, slide DDX-3028.
Q I believe, Doctor, when you were testifying about slide DDX-3028, you said you needed an honest and -- I'm sorry -- you needed to be, quote, honest and clear about the nature of etanercept, closed quote.
Do you recall that testimony generally?
11:11A A Honest and clear?
Q Yes. I wrote down that you said that: We need to be honest and clear about the nature of etanercept.
First of all, would you agree that we need to be honest and clear about the nature of etanercept?
A Yes.
Q The picture on the left, that shows a left-hand and a right-hand. Correct?
A I don't think so, it shows etanercept.
Q Right. Etanercept doesn't actually look like the picture on the right, even as simplified. Isn't that right? Etanercept has, as a bivalent protein, two left hands. Right?
A I mean, it's a molecule. The hand is a very abstract depiction anyway. To me it's a molecule. I see it as

molecule, not as a hand.
Q Right. And in etanercept the molecule, the right and left arms are not mirror images of each other. Correct?
A No. As I just said, they are related by a rotation.
11:12A Q Right. So they have as we showed in the simplified cartoon, two left hands. Correct?
A If you say so, this may be a way of depicting it.
Q Okay. So if we wanted to make even at the cartoon level that more accurate, what we'd do is we'd rotate the right green portion in the right-hand part of that slide 180 degrees. Right? So you would have two left hands rather than a right and a left?
Even at the cartoon level, if we were trying to be more accurate, that's what we would do. Right?
A Sorry, I do not understand the question.
Q I'll try again with a pointer although my track record with these is not triumphant.
You depicted here the left-hand, as it were, of the etanercept arm. Correct?
11:13A A I think actually this was done by a graphics expert, but to me this is just one extracellular region of a receptor. I wouldn't see it as hands. I mean, of course I used the analogy, I was talking about arms. But for me, this is a depiction of a molecule, of a protein.
Q Well, it's not just a protein, Doctor. Right?

I'm sorry, do you prefer "Doctor" or "Professor"?
A As you like.
Q Which do you prefer?
A "Doctor."
Q Okay. Doctor, you -- this is not just a protein, this is etanercept. Correct?
A Etanercept in my understanding is a protein.
Q Okay. And you depicted it, sir, as being -- you depicted the two arms as being mirror images of each other. Correct?
A I mean, this is a two-dimension image to me. So if you took the left part and rotate it by 180 degrees on a vertical axis you come exactly up with the picture for the right part.
11:14A Q Exactly. So if you took one of these halves and rotated it 180 degrees, that would be a more accurate depiction of etanercept. Would you agree with that?
A Yes, but I would expect that it looks exactly like it is depicted here.
Q Okay. I didn't quite hear the first part of that your answer.
A If I would, I would say as a scientist, if I performed this operation, that means the 180 degrees rotation, I would exactly come up with the picture as it is drawn here on the left.
Q We may be missing each other.
Let me start again. I take it from the title of this slide, you meant this to be an accurate representation of

etanercept. Correct?
A It's an abstract representation of course. This is not molecular detail.
Q Right.
A But so far on this level of abstraction, I think in my -- as far as I am familiar, this is an accurate representation.
Q Okay. And etanercept is not actually with respect to the two arms a mirror image of each other. Correct?
A The left is not a mirror image of the right, absolutely.
11:15A Q But in this depiction you've depicted it as mirror image. Correct?
A I do not agree. Because mathematically on this two-dimensional plane as we see here there's no distinction between the rotation across the vertical axis or a mirror representation. There's no distinction here, mathematically speaking. I'm sorry.
Q With the two left hands that we looked at a moment ago in mind, would you agree that a more accurate depiction, even at this abstract level, of etanercept would have been to have shown one of these arms rotated 180 degrees so that they're not cupped like that? Right?
A No. I get an idea what you talk about. You may talk about translation. So if I just shift the left arm to the right, then it would look different of course, but this is what my purpose I'm trying to avoid. I tried to give a more realistic

representation.

So in my understanding -- and I think every other scientist would agree -- the left part and the right part are here connected by a kind of virtual axis. Virtual because this is not in space, this is just a projection, this is only on the two-dimensional projection plane. We would have to look at the three-dimensional structures. So we need to insert a dimension then in order to then talk about what you're up to. But this is not shown here on this slide.

11:17A MR. WINTERS: Okay. Why don't we look, if we can, at DDX-3010.

Q This is your depiction of the expected binding of etanercept to soluble TNF. Correct?

A Yes.

Q And the way you've depicted this, the molecule -- it would be impossible for the molecule you've depicted here to bind a second trimer, wouldn't it? This is just going to always bind that one trimer as you've depicted it. Fair?

A No, we were just talking about rotation. And just to explain it now, I have rotated the left image by almost 90 degrees, not quite, almost 90 degrees. Okay? And now because the TNF is a trimer, you can see the difference. So I think this is quite accurate on the scientific level.

11:18A Q It's fair to say you don't have personal experience, personal experience with the TNF receptor. Correct?

A That's right, yes.
Q Have you ever done studies to investigate the signaling associated with TNF and TNF receptors in the course of your research?
A No.
Q Have you ever done studies on the structure of TNF-alpha?
A No.
Q Have you have ever done studies on the structure of TNF receptors?
A No.
Q I take it then you have no papers published on the structur of TNF-alpha. Is that correct?
A Yes.
Q And you have no papers published on the structure of TNF receptors. Correct?
A Yes.
Q Is it fair to say that your knowledge of the interactions of TNF proteins with TNF receptor proteins that you express in this case were formed by your review of information for purposes of this case only?
A Yes.
Q You talked earlier about whether or not etanercept has displayed unexpected properties and, in particular, CDC and ADCC. You've offered those opinions here. Correct?
11:19A A Yes

Q Have you ever personally conducted experiments like experimental assays which investigate CDC?
A No, I have never done such experiments.
Q Have you personally conducted experiments like experimental assays which investigate ADCC?
A No.
Q Have you done experiments where you're comparing the effects of CDC activity that are linked to differences in protein structure?
A No.
Q Have you done experiments where you're comparing the effects of ADCC activity that are linked to differences in protein structure?
A No.
Q Have you ever published any original scientific research that is looking into the effect of antibody structure and effector functions of antibodies?
A I have written a couple of publications about antibody structure and function. I do not think that -- but I'm not quite sure that this point was touched.
11:20A MR. WINTERS: Could we have Dr. Skerra's deposition at 35, lines 22 through 37?
This can't be right. Sorry,
May I just have a moment, your Honor?
THE COURT: Yes.

(There is a pause for Mr. Winters.)
MR. WINTERS: We have Dr. Skerra's deposition at page 35, line 23 through page 36, line -- what's it, Jeff? Through line 6.
11:21A MR. RURKA: Oh, this is improper impeachment.
MR. WINTERS: He says at the bottom he didn't do specific research on effector functions.
MR. RURKA: That's not what he testified. He didn't testify contrary to that today.
THE COURT: Hold on.
You know what, you can go ahead with it.
I think the question was: Have you ever published any original scientific research that is new looking into the effect of a structure of effector functions.
MR. WINTERS: Why don't we take that down and I'll just ask the question.
THE COURT: Go ahead.
BY MR. WINTERS:
Q Doctor, do you recall if you published any original scientific research looking into the effect of antibody structure and the effector function of antibodies? Have you done that?
11:22A A Looking back 30 years, I don't think so, but I would have to have a closer look at my publication list.
Q Okay.

A The question in the deposition was related to my Ph.D thesis.
Q I'm sorry?
A The question in the deposition was referring to my Ph.D work.
Q Okay. With respect to forming your opinions in this case, you did not independently determine the amino acid sequence of etanercept to form your opinions, did you?
A What do you mean by "independently determine"?
Q Did you verify -- did you look to any document -- well, you got -- withdraw that.

You got the number of amino acids in the TNF portion of the etanercept molecule from counsel. Correct?

11:23A A Yes.
Q And you didn't then independently yourself go out and confirm whether what they told you was correct, did you?
A No, I didn't have access to original documents that would have described the structure of etanercept at this level.
Q And for purposes of your opinions about unexpected results as you expressed them in your report, you understood that the p75 portion of the etanercept molecule had 185 amino acid residues. Correct?
A 185 or 235.

MR. WINTERS: Could we have, please, Dr. Skerra's report at page 26, paragraph 78 up.

Bill, could you highlight the last sentence, please.
Q You didn't say in your report, Doctor, "185 or 235," did you? You said, "I have been informed that the extracellular domain" -- let me stop there. Extracellular domain -- well, let me start again.
11:24A What you said was: "Additionally, I've been informed."
That's by counsel, correct? You've been informed?
A That's the information which I received, yes.
Q That the extracellular domain of the TNF receptor used in etanercept has 185 amino acid residues.
That's what you told us in your report. Correct?
A Yes.
Q And --
MR. WINTERS: Bill, could you highlight the sentence just before that, please.
Q And you set forth that understanding on which your opinions were based in specific contrast to the number of amino acid residues in the TNF receptor extracellular region. Correct? That's what you were communicating in that sentence that we just highlighted?
A Excuse me?
Q In the last sentence you informed us what the molecule that you analyzed looked like in terms of the number of amino acid -- number of amino acids in the TNF portion. Correct?

11:25A A Yes.
Q And in the sentence just before, you told us how many amino acids were in the extracellular region of the p75 TNF receptor. Correct?
A About 235 amino acids, yes.
Q Right. And that fusion protein, an IgG portion and a TNF portion with 185 amino acids residues was the molecule you considered in forming all your opinions that you've expressed here today. Correct?
A In principle, yes.
Q But, in fact, sir, etanercept does not actually have only 185 amino acid residues in the TNF portion, does it?
A No, I learned later that the portion is larger, but this doesn't change my opinion.
Q On that subject, suppose -- you say it doesn't change your opinion. Let's look at that. Suppose you took the etanercept molecule that you told us you looked at in your report with 185 amino acids rather than the correct number, and up added 50 amino acids residues between the TNF receptor and the IgG portion, so now you've got the full 235.
11:27A You agree, don't you, that that fusion protein with the full p75 TNF receptor sequence would be more likely to bind different TNF trimers as opposed to binding one TNF trimer. Isn't that correct?
A No.

MR. WINTERS: Bill, could we play, please, the clip at deposition page 275 leading with line 21 running through 276, line 3.

(An excerpt of a deposition is played in open court; and stopped.

Q And the aggregation you're referring to in that clip, sir, is the physical or biological phenomenon in which the bivalent protein is binding to separate TNF trimers and not one. Correct?

11:28A A But I understood the question in a different way. I think the question was talking about adding additional 50 amino acids, and this is what I understood adding over the natural biological situation.

So my assumption was, I have this extracellular portion of the receptor, and this is a biological molecule as it was made by nature, so it's obvious made to bind TNF-alpha. So in this picture it's not really necessary to know the precise number of amino acids. I mean, I confirmed the literature and so far as I looked at the Dembic paper and I have seen that all four domains of the receptor must be present. And so I watched at this extracellular region like a natural biological molecule. Okay?

But then the question is: What happens? And I mean if the natural molecule is a few amino acids more or less, the assumption is that this chain of amino acids folds into

something which we would call an immunoglobular domain, and the immunoglobular domain is like a potato-shaped molecule, that means as we have seen for the TNF-alpha, it's folded and it forms a functional state.

11:29A Now, if I add something artificially, then we come up with a different situation.

Q Right. And the question you were asked at your deposition, sir, asked you to take the molecule that you've said you actually looked at, which we've displayed in your report, and added 50 amino acids to it between the hinge and the TNF portion, what would you expect that to do?

And what you told us at the time -- just at the time, was that that molecule would be likely to cause more aggregation. Isn't that what you told us?

A Yes.

Q And you did not correct that testimony in your transcript, did you, sir?

A No, but I believe the topic was further discussed in my deposition, and I think I provided additional opinion in this regard.

Q And you did not -- withdraw that.

And you did not provide a supplemental report correcting your report, did you, sir?

11:30A A What do you mean?

Q You gave us a report at one time in the case. Correct?

A Yes.
Q At no point did you provide us another version of that report correcting anything you had said in the initial report. Correct?
A No.
Q That's wrong?
A I did not submit another report or a corrected version except for minor corrections which I produced.
Q Okay. Would you agree that a fusion protein has to aggregate in order for it to have effector functions?
A It depends on the effector function. But if you talk about CDC and ADCC, I mean, there are more effector functions out there like plasmid, half-life extension and things like that. With regard to CDC and ADCC it is my understanding that I need multiple, that means many copies of the Fc portion of an antibody or a fusion protein in order to elicit CDC or ADCC.
11:31A Q Let me just ask perhaps a better question so the record is clear: Would you agree that a fusion protein has to aggregate in order for it to display CDC and ADCC?
A Yes.
Q Do you agree that Dr. Capon expected in his first CD4 fusion constructs discussed in his 1989 article to retain both ADCC and CDC?
A I don't know about his expectations.
MR. WINTERS: Could we have JTX-58 at page 1, the

right column and the second first full paragraph up, Bill. So the right column, the other right column.

Perfect.

Q And do you see, sir, about five lines down it says: (Reading) Second, we wanted to incorporate functions such as Fc receptor binding, protein A binding, complement fixation and placental transfer, all of which reside in the Fc portion of the IgG.

11:33A Do you see that?

A Yes.

Q Would you agree that that would have told the ordinary artisan at the time that Dr. Capon expected to retain CDC and ADCC in his fusion constructs?

A I would rather call it a desire. I do not know what he honestly expected. But, I mean, obviously this was one of the questions which was investigated in the study.

Q Okay. And Fc receptor binding, that functionality is triggered by the hinge between the -- excuse me -- it's triggered by the junction between the hinge and the CH2. Correct?

A I'm not so sure whether this was known at the time at this level of detail. At least it was clear that the Fc receptor interaction was somewhere in the region of the CH2 domain.

Q And the functionality -- sorry -- the portion of the structure that triggered the functionality that is CDC, that

resided in the CH2 domain. Correct?
11:34A A You're now talking about CDC?
Q Yes.
A I rather thought CDC would involve the protein region. But anyway, it's the Fc portion, I mean without now discussing individual amino acids.
Q And as you sit here today, you don't know where in terms of the structure the functionality -- withdraw that.
As you sit here today you don't know where in the structure the domain is that triggers the functionality that is CDC? You don't know that?
A I know that it's in the Fc region. Where exactly, I mean, I think there was a publication by Greg Winters' group. One could look it up. That was known at the time. But I can't tell you the individual amino acids by heart.
Q Can you tell me the region, sir, without --
A It's the CH2 region, which actually translates on its N-terminal side into the hinge. Somewhere in this region, those -- both the binding activity for the Fc receptor and the binding activity for C1q is located.
Q So focusing just now on CDC, can you tell me in what domain in the Fc that functionality -- where that functionality is triggered?
11:35A A I think it was CH2 domain and part of the hinge region.
Q And, in fact, Dr. Capon in his contructs actually found

binding to Fc receptors, correct, in that 1989 paper?
A I think so.
Q Let's remove the doubt.
MR. WINTERS: Could you put up JTX-58 page 5, the left column, and there's a paragraph that begins: "Thus, our immunoadhesins bind well to Fc receptors."
There you go.
Q Okay. Maybe we can clear up what you said with some uncertainty on your part, Doctor.
Dr. Capon reported here, correct --
MR. WINTERS: Bill, if you can highlight "As far as is known." No, the sentence that begins "as far as is known."
Perfect.
11:36A Q (Reading) All the critical contact residues for C1q binding reside in the CH2 domain in the heavy chain.
Let's stop there. C1q binding is a step in the process that leads to CDC. Correct?
A Yes, that's general --
Q What he's -- I'm sorry, I may have talked over you. What was your answer?
A That's the general understanding, yes.
Q And what he was reporting there is in terms of what was known in the art at the time, and he provides a reference, the critical contact residues, all of them were in the CH2. Do you see that?

A The critical contact residues, yes.
Q You don't have a basis to dispute that that was known in the art at the time, do you, sir?
A No.
Q Okay.
MR. WINTERS: Bill, if you could highlight that first sentence: "Thus, our immunoadhesins..."
Q That Fc receptor binding, that is an early step in the biological process that yields ADCC. Correct?
11:37A A Yes.
Q And so what he found there was if his constructs -- withdraw that.
MR. WINTERS: Perfect, thank you.
Bill, keep that up.
Q Dr. Capon was surprised that his constructs did not bind C1q, wasn't he? His article reflects that?
A He may have expressed his opinion in the discussion later on.
Q Yeah. It says right here: "It's perhaps surprising that they did not bind" --
A It's perhaps surprising, yes. It says "perhaps."
Q And the reason he was surprised was that, and he explains in it the next says: "As far as is known, all of the critical contact residues for C1q binding are present in the CH2 domain correct.

11:38A A Yes.
Q So what the ordinary artisan would have understood from that was, because Dr. Capon's construct retained the CH2 domain, he expected to get C1q binding. Correct?
A No.
Q Isn't that what he says? It's perhaps surprising that they don't bind C1q, and then he tells the ordinary artisan why?
A Yes. He was surprised but I would not have been surprised, and other scientists also would not have been surprised because it was also known at the time that the strengths of binding between the CH2 domain or, let's say, the Fc part of an immunoglobulin and the C1q component of the complement system is very weak, and you need to bind several copies of C1q at once in order to really demonstrate the binding and also in order to elicit the CDC. This was well-known at the time. I don't know why he doesn't refer to this knowledge in this publication.
11:39A Q As far as you're aware, this publication was the very first IgG fusion construct published anywhere. Right?
A To my knowledge, yes. And actually I even picked this publication up during my Ph.D thesis and presented it in journal club, so I'm well aware of this publication and its role in science, yes.
Q You're not holding yourself out, sir, are you, as a greater expert in ADCC or CDC than Dr. Capon, are you?

A No.
Q You agree that when the patents were filed there were no reported experiments involving IgG fusions in which scientists tested different length receptors to see what effect receptor length had on effector function?
MR. WINTERS: And, Bill, you can take that down.
Q Do you need the question back?
11:40A A Does this refer to this publication, or could you please repeat your question?
Q Do you agree, sir -- so we have the Capon publication down now -- that whether the patents were filed there were no reported experiments involving IgG fusions in which scientists tested different length receptors to see what receptor length had on effector function.
Do you agree with that?
A No.
Q What publication do you have in mind?
A I think Capon used different constructs, if I remember correctly, where he used either all four domains of the CD4 receptor or just two domains.
MR. WINTERS: Bill, if we could put up in that --
Q Other than Dr. Capon's article that you just referenced, are you aware of any other publication that looked at that issue?
11:41A A I am not sure. Maybe Traunecker. There were variations

with regards to receptor lengths, but I may agree to the extent that there were no systematic investigations.

Q And that's the question I'm asking, sir. Other than the Capon article, which we'll look at again in a moment, are you aware of any reported experiments involving IgG fusions in which scientists tested different length receptors specifically to see what that different length, what effect that different receptor length had on effector function?

A I'm not aware of a publication that investigated this specific aspect.

Q The same question --

A At that point in time.

Q The same question with respect to antibodies. Any reports in the literature looking at varying antibody length to see what effect that had on effector function?

A No, I do not agree with that. Because in the area of antibodies, there were antibodies known which correspond to deleted portions of full-length antibodies. These were the so-called Bence/Jones proteins or myeloma proteins, and those were known at the time where part of the hinge region, for example, or other parts of the antibody were shortened.

11:43A Q Let's take a look at Dr. Capon's experiments as he referenced them, and just to -- let's see if we can agree on something.

Those were IgG fusion constructs. Correct?

A Yes.
Q They had an IgG portion and a receptor portion. Correct?
A Yes.
Q Etanercept has an IgG portion. Correct?
A Yes.
Q And the receptor portion. Correct?
A Yes.
Q Let's take a look --
MR. WINTERS: Bill, if you could put up -- well, before we do that.
Q You mentioned in his 19 -- that his 1989 paper tested two different constructs. Correct?
A I believe so.
Q Okay.
MR. WINTERS: Let's take a look together and we can confirm for the Court.
Bill, could you put up JTX-58 at page 2, Figure 1 and the legend. Figure 1 is up at the top left. Great.
Q These are the constructs you referred to earlier. Correct?
11:44A A Yes.
Q And, in fact, he did look at constructs that had two different lengths. Right? One of the constructs had only two domains from the CD4, and this is in the figures at the top of the document. Right? There's a construct there. The last -- the second to the last line, there's two CD4 domains there.

Right?
A If I can help you. Yes, exactly. So here we see two domains of the CD4 and here we see four domains of the CD4 receptor.
Q Those were his two constructs. Correct?
A Yes.
Q And they were otherwise the same with respect to the IgG portion. Correct?
A That's what I understand from his presentation, yes. I mean, the individual amino acid sequences are not shown here but fundamentally I would say this is correct.
Q When you say the individual amino acid sequences aren't shown --
MR. WINTERS: Let's take a look, Bill, if we could, at the legend, four lines up from the bottom.
11:45A Perfect.
Q In fact, Dr. Capon told the art how many amino acids were in the two respective constructs. Correct?
A Yes.
Q And his construct with two domains, that for the Court is the construct that's depicted schematically in the line second to the last, and the construct with four is depicted schematically in the very last sentence. And what Dr. Capon reported was, the two-domain construct had 180 amino acids in that portion of the construct. Right?

A Yes.
Q And the four-domain construct had twice that many, a little over twice that many; 366 residues. Correct?
11:46A A Yes
Q And it's true, isn't it, that Dr. Capon found experimentally in this publication that neither construct showed steric hindrance, and that both caused an agglutination. Isn't that right, sir?
A I would have to have a look at the details. I do not remember whether he did all this experiments with both types of constructs, or whether he did a side-by-side comparison in all of his experiments.
Q Let's take a look and let's make that clear, if we can for the Court.
MR. WINTERS: Bill, could you call out JTX-58 at 2, it's the right column. gp-120 heading, the last two sentences please, and just blow that up.
Q So he if says: To confirm the bivalent nature of 2-gamma-1 and 4-gamma-1 -- that's two constructs we just looked at. Correct?
11:47A A Yes.
Q That's the one with two domains and the one with the four domains?
A Yes.
Q Okay. (Reading) We examined their ability to agglutinate

sheep red blood cells coated with gp120.

He goes on to say: (Reading) Both CD4 immunoadhesins, but not soluble RCD-4, agglutinated the cells, showing that binding to gp120 molecules on different cells is not sterically hindered.

Let me see if I can translate that into perhaps lay language and you tell me if I'm getting that wrong.

What he said there, Doctor, is that he tested both of his constructs to see if they agglutinated. Correct?

A Yes.

Q And one construct had in the receptor portion 180 amino acids, and the other had 366. Correct?

A Yes.

Q And he found that notwithstanding that those two receptors -- I'm sorry. He found that in hose constructs, notwithstanding that one receptor portion was half the length of the other, they both agglutinated. Correct?

11:48A A Yes.

Q Okay. In terms of -- and "agglutination" means the ability to cross-link separate molecules. Correct?

A This is the red blood cell experiment which I actually also had in my presentation, and that in this case means binding to two copies of gp120 molecules in a monomeric state but absorbed to different red blood cells.

Q And just so the record is clear, what agglutination meant

in this context was, his constructs were binding to two separate sheep red blood cell molecules. Correct?
A Yes.
Q Thank you.
Now let's talk about the arms of etanercept.
Those have, in terms of the receptor portion, 235 amino acids. Correct?
A Yes.
Q That falls right smack in the middle of the range as against what Dr. Capon tested. Right?
11:49A A In counting the amino acids, yes, but this is not the only aspect for a protein biochemist.
Q Let's talk about that subject.
You explained in your report, Doctor, didn't you, you explained why you thought an ordinary artisan at the time would have expected what you call the much smaller arms of etanercept to bind TNF in the same trimer. Correct?
A I think I used more properly the adjective "slim."
Q Okay. Let's take a look.
MR. WINTERS: Bill, if could put up paragraph 78 through 80 of Dr. Skerra's report. I think that's at page 26 of the PDF.
11:50A Q Now, let's just walk through at least what you told us in your report.
So this is where you report how many amino acids the

p75 TNF receptor had in the extracellular region and how many amino acids the molecule you utilized had in the receptor portion. Correct?

MR. WINTERS: Bill, could you bring up the next one.

Q And you talked here about the ordinary artisan having had expected more steric hindrance, and you give some reasons. Right?

A Yes. But here talking about the FAB arms of the antibody.

Q Right.

MR. WINTERS: Bill, if you could bring up the last...

Q And here what you said was: (Reading) On the other hand, an ordinary artisan would have expected much less steric hindrance between the much smaller arms of a bivalent TNF receptor fusion protein. And you say, you go on to say: (Reading) In the absence of such hindrance, two arms of the bivalent TNF fusion protein could bind the two TNF molecules in one TNF trimer.

11:51A In summary, what you're saying there, Doctor, is that because -- and I'll use your words -- the etanercept molecule you were looking at had much smaller arms, the ordinary artisan would expect those two smaller arms to bind one TNF trimer rather than two separate molecules. In summary, that's what you're communicating there?

A Yes. Small, but in terms of spatial dimensions. And this is why I also used the term "slim," compared with bulky arms of

a FAB fragment.
Q Right. And in terms of the amino acid length of etanercept as compared to the amino acid length of the constructs Dr. Capon analyzed, etanercept falls right smack in the middle. Right?
A May I clarify a point, please?
Q I would prefer you just answer my question, if you could.
In terms of the number of amino acids in the constructs Dr. Capon assessed as against the number of amino acids actually in etanercept, that's right in the middle. Isn't that right?
11:52A A In terms of the number, yes.
Q Okay.
MR. WINTERS: Give me one second, Doctor.
May I have just one second?
THE COURT: Certainly.
(There is a pause for Mr. Winters.)
11:55A Q We're going to find something, Doctor. I'm going to move on to a different --
THE COURT: Do you want to take a few minutes?
MR. WINTERS: We'll come back to it. Thank you, your Honor, I appreciate that.
THE COURT: Okay.
BY MR. WINTERS:
Q We've been talking about, Doctor, your opinions about

etanercept binding to a single TNF trimer. Let's talk about that trimer.

Would you agree that in August of 1990, the three-dimensional shape of the extracellular region of the p75 TNF protein -- withdraw that.

In terms of the p75 TNF receptor portion of this invention, would you agree that at the time of the invention the three-dimensional shape of the receptor portion of etanercept had not been determined by exray crystallography?

11:56A A That's my understanding, yes.

Q Would you agree that at that point, what was known about the p75 TNF receptor portion of this invention was the amino acid sequence?

A Actually the nucleotide sequence, the DNA sequence, and the amino acid sequence was determined by inference from the DNA sequence, yes

Q And you've been talking about the nature of TNF receptor binding and TNF-binding. Had the precise nature of that binding been determined by exray crystallography by August of 1990?

A No.

Q Had the amino acids in the extracellular region of the p75 TNF receptor, in terms of where that binding occurs, had that been experimentally confirmed as of August 1990?

11:57A A Not that I know of.

Q An antibody binds to an antigen by binding to a specific region on the antigen called an epitope. Correct?
A Yes.
Q And would you agree that at the time of the patents, the ordinary artisan would have expected that antibodies that bind to TNF trimers, so antibodies now that bind to TNF trimers, would tend to aggregate?
A No. The default assumption would have been that the antibodies would have taken advantage of the avidity effect and form a one-to-one complex, that would have been the default assumption unless one would, let's say, further think about it.
MR. WINTERS: Could we have, please, Dr. Skerra's report at page 26 of the PDF, paragraph 79, the last sentence.
Q Isn't that what you're communicating here, Doctor?
11:58A A Yes, and that's what I also presented in my presentation.
Q I'm sorry?
A That's what I also explained in my presentation.
Q So you'd agree then that it was known in the art at the time that antibodies that bind to TNF trimers would tend to aggregate. Fair?
A No, at the time those antibodies were not known.
Q I'm sorry?
A The antibodies only became known much later.
Q Could you read, please, into the record the sentence we've highlighted?

A (Reading) The cross-linking of two TNF trimers via one antibody molecule further leads to formation of large antibody TNF trimer aggregates (complexes).
Q And that's still your testimony?
A Yes.
Q By the way, you used an analogy or metaphor -- I can never keep the difference between those straight -- but earlier you talked about if you had a box you were trying to lift.
11:59A A Yes.
Q And you grabbed one side of the box, your other arm would grab the other side of the box. Do you recall that?
A I grabbed the handles, yes.
Q Right.
A And the handles would be the epitopes.
Q Right. So in terms of what was known at the time, in terms of how a bivalent protein bound its target, that's too left hands. Right? Not a left and a right.
A But the handles do not distinguish left or right-hand.
Q Okay. Let's just take this step-by-step.
A Yes.
Q At the time the bivalent protein molecule would have had two left hands, not a left and at right. Correct?
A Of course the analogy has its limitations, correct.
Q And in terms of what was known at the time with respect to how etanercept could have been expected to bind to its target

trimers, to its target TNF -- well, withdraw that. Let me take it out of that context.

12:01P In terms of how a TNF receptor bound to TNF -- and now we're on the same page with the two left hands -- the precise binding site in the trimer and TNF, that had not been determined. Correct?

A No, it was not determined.

Q And the precise place along the TNF receptor that bound to the TNF trimer, that hadn't been determined either. Correct?

A I agree.

Q And the shape of that, you had talked about grabbing a box. The shape of that binding, that had not been determined either, correct, the confirmation?

A The shape of the TNF trimer was known, but of course it was not known what is the precise shape of the receptor for it. So that piece of information was missing.

Q Right. And it wasn't known where -- it wasn't known precisely where along the TNF receptor that binding occurred. Right?

12:02P A That's what I said before, yes.

Q Okay. Would you agree that at the time of the patents, it was known that each arm of an antibody bound to an epitope on one TNF molecule on two different TNF trimers?

A I do not think so because the antibodies were not known at the time.

MR. WINTERS: Why don't we take a look, if we could, please, at Dr. Skerra's report, PDF page 26, paragraph 79.

Q And you say, there's a sentence in the middle, Doctor --

MR. WINTERS: Could you highlight that, Bill, "Therefore, one..."

12:03P Q Would you read that sentence into the record, sir?

A (Reading) Therefore, one FAB arm of the antibody would be free to bind to another TNF molecule in another TNF trimer, cross-linking two TNF trimers.

Q And the cross-linking you're referring to there, that's like the agglutination we saw earlier in the sense that one arm of the bivalent protein is binding one target and the other arm is binding another target. Right?

A The agglutination we talked about before referred to cells. Here we are talking about protein molecules. Here I would call it aggregation.

Q Okay. But in terms of the way the arms are binding, what you're communicating here is that one arm of the bivalent protein is binding one target, and the other arm of the bivalent protein is binding the same kind of target, but just a different one. Correct?

A Yes, it's the Mode 1 which I referred to in my presentation, yes.

12:04P Q And this is still your testimony. Yes?

A Yes.

Q Would you agree that there are, as a matter of theory, three different kinds of modes of binding?
A That's the way how the expert, Dr. Naismith, presented it. I mean, if I would think about it I may even envisage more modes of binding, but I think I could agree to Dr. Naismith's view and the principle existence of these three modes of binding.
Q And at the time it was known that antibodies bound in mode one. Correct?
A Under certain circumstances.
MR. WINTERS: Could we have, please, Dr. Skerra's report at page 18, paragraph 63. And there's a sentence that that begins about halfway down: "Due to this steric hindrance, one antigen binding site of the antibody would remain free to bind to another TNF trimer, which leads to cross-linking of two TNF trimers."
12:05P Q You're describing mode one binding there. Correct?
A Yes.
Q And that was known at the time by the ordinary artisan. Correct?
A That it can happen. It was known, yes.
Q And that, in fact, for antibodies it was known that that was typically what antibodies did. Fair?
A No, I don't think so, because for antibodies the avidity effect was known. So that means if the antibody has the chance

to bind epitopes on one and the same particle, it would do so, because this also was explained in Dr. Roitt's textbook and that was the general expectation at the time.

Q And you just explained here --

MR. WINTERS: Bill, back up on the slide, back up on the screen. DDX-3024.

12:06P Q This is the Crothers article from 1972. Correct?

A Yes.

Q And you discussed the sentence highlighted in yellow there. That reported a theoretical conclusion. Correct?

A Based on experimental evidence which was referenced in this publication.

Q Okay.

MR. WINTERS: And if you could move that up, Bill.

I would like to focus on a sentence that I don't think you discussed.

Bill, if you could highlight the next sentence.

Q Could you read that sentence, Doctor, into the record?

A Certainly. (Reading) That the opposite appears sometimes to be experimentally the case means that special features favoring agglutination reactions must be present in these instances.

This is what Crothers and Metzger say.

Q And what you're referring to there is the behavior of antibodies. Correct?

A No, not exactly. They referring to the exception.
12:07P Q We'll talk about whether that's the exception. But the experiments they're referring to there are experiments involving antibodies. Correct?
A But in their first sentence they also referring to antibodies.
Q The experiments that they're referring to there concern antibodies. Correct?
A Yes. Yes.
Q And it was correct, was it not at the time, that in terms of experimental results involving antibodies, they normally reflected agglutination or aggregation. Correct?
A No.
Q That was not known at the time by the ordinary artisan, wasn't it?
A No.
Q What publication or publications, if any, did you have, do you have in mind when you say "no"?
A I think we can just use this publication and go five pages further down where Crothers and Metska quote to experimental studies which they can perfectly explain that theory.
12:08P Q We will return to that then.
In terms of the three theoretical modes of binding, a consequence of Mode 1 binding is aggregation. Correct?
A Yes.

Q And antibodies have a Y-shape. Yes?
A Fundamentally, yes.
Q With binding sites on each arm of the Y?
A At each tip of the Y actually.
Q Yes?
A Yes.
Q Etanercept also has a Y-shape. Correct?
A Yes.
Q With binding sites on each arm of the Y?
A Yes.
Q Would you agree that as of August 1990, there were no reported experiments showing that TNF receptor IgG fusions would behave differently than an antibody and not cause aggregation?
A Yes.
Q As of August 1990, the positioning of etanercept's arms in relation to TNF trimers was not known. Correct?
12:09P A Yes.
Q There was, however, publicly available data on the effector function reported in the CD4 IgG fusion protein art. Correct?
A Some information, yes.
Q And Dr. Capon's 1989 article talked about that. Yes?
A Yes.
Q And the Traunecker article talked about that. Correct?
A Yes.

Q And the Byrn article talked about that. Correct?
A Which one?
Q Byrn 1990.
A I'm not sure whether I had a closer look at this article.
Q Okay. Maybe we can -- you're not -- as you sit here you don't think you're familiar with that article?
A No.
Q How about the Gregorson (phonetic) article. Are you familiar with that?
A Which year?
Q Gregorson?
A Which year.
Q I think that's 1990.
A I think, yes, I'm familiar with that article, I believe so.
Q And would you agree that the ordinary artisan would have understood in the aggregate that art to teach that if you retain the IgG1 component hinge-CH2-CH3, one should expect that construct to have -- you know, to show CDC and ADCC?
12:10P A No.
Q You don't think that's a fair summary of that art?
A I don't think so.
Q Which of those four articles disproves that in your view?
A I think the experimental evidence given in those articles was incomplete. I mean, what was to be deduced from this articles was that the Fc portion of the fusion protein would

have binding activity to the Fc receptor, and that it would also in principle have binding activity even though to low C1q, but this condition alone is not sufficient to elicit CDC or ADCC because it is necessary to have these high molecular weight or higher order aggregates in order to elicit the cellular response of the ADCC or the complement response which is the CDC. So the mere binding affinity is not sufficient.

12:11P MR. WINTERS: Why don't we, if we could, look at JTX-56, that's Byrn article at the abstracts.

And there's a sentence that begins -- yeah, perfect.

"Here we show..." Exactly.

Bill, could you just highlight that to the end of the sentence.

Thanks. All way to "Their surface..."

Q In fact, Doctor, didn't this Byrn publication show with experimental evidence that their CD4 IgG fusion construct actually demonstrated ADCC?

12:13P A In the case of a membrane-bound antigen, gp120 on the surface of HIV infected cells, I agree.

Q And we've looked at Dr. Capon's 1989 article. You'll agree that he expressed in that article the expectation that his construct would both bind C1q -- you agree with that. Right?

A Yes.

Q And that it would show Fc receptor binding. Correct?

A Yes.

Q And the binding of C1q is the first step that leads to -- is an early step that leads to CDC. Correct?
A It can lead to CDC, yes.
Q And the Fc receptor binding is an early step that can lead to ADCC. Correct?
A Yes.
Q And how about the Gregerson article; would you agree that that article proved that an IgG CD4 construct actually demonstrated ADCC and CDC? Would you agree with that?
12:14P A In the context of HIV-infected cells.
Q Was that a "yes"?
A Yes.
Q Okay. And this is my last question before we turn subjects in case the Court has a lunch preference. But would you agree that at the time of the patents, there was not a single prior art reference that tested an IgG fusion protein for effector functions and demonstrated experimentally that there were none?
A Could you please repeat the question?
Q Yes. Would you agree that at the time of the patents, there's not a single prior art reference that tested an IgG fusion construct for effector functions and found that it did not have any?
A Didn't we just talk about the Capon paper where those effector functions were not detected in some of the experiments?

Q You're talking about Capon 1989?
12:15P A Yes.
Q And his construct had a CH1. Correct?
A Yes.
Q I may have talked over you. His construct retained the CH1 region. Correct?
A I guess so, yes.
Q And etanercept does not have a CH1 region, does it not?
A Not to my knowledge.
Q So with your help I'll ask perhaps a better question.
A Okay.
Q Would you agree that at the time of the patents, there was not a single prior art reference that tested an IgG fusion construct that had the following part of IgG: Hinge-CH2 and CH3, and demonstrated experimentally that there was no effector function?
A Yes.

MR. WINTERS: If this is a logical time for the Court to have lunch, or I can keep going.

THE COURT: Hold on one moment, let me just check.

That would be a fine time to break.

Let's take our lunch break at this point. You may step down. Be mindful.

And we'll see you back here in an hour. Thank you.

12:16P THE DEPUTY CLERK: All rise.

(Witness temporarily excused.)

(A luncheon recess is taken.)

(The PM Session of this day's proceedings is found in a separate transcript booklet.)

ooOoo